ARA 290 - DMO

A phase II Clinical Trial on the use of ARA 290 for the treatment of diabetic macular oedema

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STATISTICAL ANALYSIS PLAN

Final 1.0

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This document and all preceding versions will be stored in the Trial Master File for this trial

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1. BACKGROUND AND DESIGN

The hypothesis tested is that ARA 290, when administered subcutaneously at 4mg on a daily basis for 12 weeks, due to its anti-inflammatory, anti-apoptotic and neuroprotective effects, will be of therapeutic value to patients with diabetes mellitus and diabetic macular oedema.

This will be an interventional, exploratory, investigator led, pilot study with the aim of determining if ARA 290 administered at a daily dose of 4mg subcutaneously for 12 weeks to patients with DM and severe DMO (central retinal subfield thickness measured with spectral domain optical coherence tomography of $\geq$ 400 microns), will have a beneficial effect on improving BCVA, reducing central subfield thickness, increasing central retinal sensitivity and retinal perfusion, increasing tear production and improving quality of life with no adverse events. Data obtained in this pilot study will be used to inform future larger studies.

The primary objective is to determine whether ARA 290 has a beneficial effect on BCVA in people with DM and DMO.

The secondary objectives are to determine whether ARA 290 administered at a daily dose of 4mg subcutaneously for 12 weeks to patients with diabetes mellitus and DMO can improve vision (as determined by the % of participants with a ≥ 10 and ≥ 15 ETDRS letter gain), reduce central subfield thickness, increase central retinal sensitivity, increase tear production and improve retinal perfusion and quality of life with no deleterious side effects. The effects of ARA290 on the systemic and metabolic control of participants will be also evaluated in an exploratory manner.
ARA 290 antibodies will be determined as, if they were to develop in people undergoing this treatment they could have an impact on the potential subsequent response to it.

Inflammatory markers will be evaluated to investigate the potential anti-inflammatory effect of this treatment. Carbamylated albumin will be obtained as an additional measure of renal function and metabolic status and glycosylated albumin will be obtained as a confirmatory marker of glucose control.

This is a prospective, open label, interventional, single centre, investigator led, phase II study to examine the effect of ARA 290 on DMO in patients with type 1 or 2 diabetes and central retinal subfield thickness of $\geq$ 400 microns.

The study intervention is a subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks

Patients will be eligible to participate in the study if they fulfil the following criteria:

Inclusion criteria:

1. Diabetic retinopathy and centre involving DMO with a central subfield thickness of ≥ 400 microns, as determined using SD-OCT.
2. ≥18 years of age
3. Clear media and naïve to previous treatments for DMO

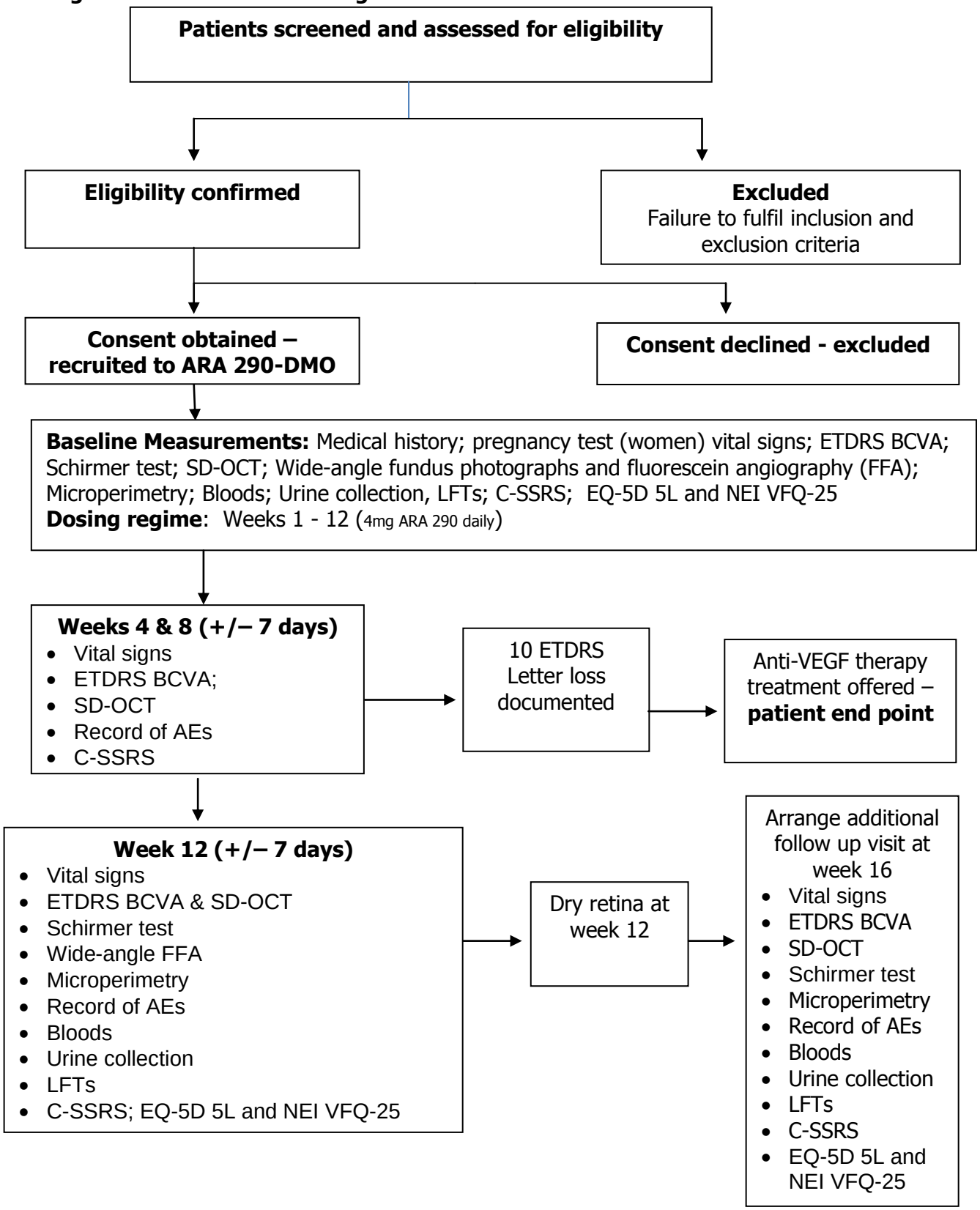
Exclusion criteria:

1. Macular oedema related to other retinal disease
2. Hazy media that prevents adequate retinal imaging
3. Allergy to fluorescein
4. Previous treatments for DMO
5. DMO with central subfield thickness of < 400 microns
6. Patients on local or systemic steroids
7. Use of erythropoiesis stimulating agents within the two months prior to screening or during the trial
8. Treated with any other investigational medication or device within 60 days
9. Pregnant women, women who have not yet reached the menopause (no menses for ≥ 12 months without an alternative medical cause), who test positive for pregnancy, or who are unwilling to take a pregnancy test prior to trial entry or are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial.
10. Men who have a female partner and who are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial.
11. Female patients who are breastfeeding will be excluded.
12. Active proliferative diabetic retinopathy (PDR) requiring treatment.
13. Patients with other eye diseases besides diabetic retinopathy
14. Patients who are unable or unwilling to commit to the study schedule of events
15. Serious illness that is likely to affect the patient's ability to complete the study

Any patient showing a clinically significant improvement between the initial screening and presenting for the first screening/baseline visit may no longer be eligible for the study and will be recorded as a screen failure and will not be entered on to the study.

The trial is summarised in Figure 1.

Figure 1. Trial schematic diagram



Full details of the background to the trial and its design are presented in the protocol.

2. OUTCOME MEASURES

2.1 Primary outcome measure

Changes from baseline to week 12 (+/– 7 days) in best corrected distance visual acuity.

2.2 Secondary outcome measures

Changes from baseline to week 12 (+/– 7 days) in:
1. Central subfield thickness
2. Central retinal sensitivity
3. Retinal perfusion
4. Tear production
5. Patient reported outcomes
6. ARA 290 antibodies

.
Adverse events
% of participants with ≥ 10 ETDRS letter gain
% of participants with ≥ 15 ETDRS letter gain

2.3 Exploratory analyses

Changes from baseline to week 12 (+/– 7 days) in:

1. Inflammatory markers
2. Carbamylated and glycosylated albumin

2.4 End of trial

For the purposes of submitting the end of trial notification to the Sponsor, MHRA and REC the end of trial will be considered to be when database lock occurs for the final analysis.
The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC)
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Mandated by the Sponsor (e.g. following recommendations from the Data Monitoring and Ethics Committee (DMEC)
- Funding for the trial ceases

The REC that originally gave a favourable opinion of the trial and the MHRA who issued the Clinical Trial Authorisation (CTA) will be notified in writing once the trial has been concluded or if terminated early.

3. DATA

3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are described in the trial protocol.

A copy of the CRF is presented in the Trial Master File.

3.2 Data completion schedule

The following table describes the time points for completion of clinical record forms.

Table 1. Data Completion Schedule

	Screening / Baseline	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks*	4 weeks post drug termination**
Consent	✓						
Pregnancy Test	✓						
Medical History	✓		✓	✓	✓	✓	
Medications	✓		✓	✓	✓	✓	
Vital Signs***	✓		✓	✓	✓	✓	
Distance Visual Acuity	✓		✓	✓	✓	✓	
Microperimetry	✓				✓	✓	
Schirmer Test	✓				✓	✓	
SD-OCT	✓		✓	✓	✓	✓	
Wide-angle FFA	✓				✓		
Blood sample for ARA 290 antibodies, immune markers, carbamylated and glycosylated albumin	✓				✓		
Blood sample for full blood cell count	✓				✓	✓	
Liver function test (LFT)	✓				✓	✓	
Urine Sample	✓				✓	✓	
Adverse Events		✓	✓	✓	✓	✓	✓
VFQ-25	✓				✓	✓	
EQ-5D-5L	✓				✓	✓	
C-SSRS	✓		✓	✓	✓	✓	
Telephone check		✓					✓

* 16 week visit will take place only if the retina is found to be dried and the DMO has resolved at week 12
** 4 week post study drug termination telephone check will be completed for patients who withdraw from the trial/study drug prior to 12 weeks, or at 12 weeks, and who do not need to attend the 16 week visit.
*** Vital signs: height (first visit only); weight; heart rate; temperature; blood pressure, oxygen saturation, BMI

3.3 Data verification

Data verification, consistency and range checks will have been performed at the data entry stage by the CTU, as well as checks for missing data (copies can be found in the Trial Master File). Additional range, consistency and missing data checks will be performed, as appropriate, when the analysis is performed (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Given the thorough nature of our follow-up procedure we expect the issue of missing data to be relatively minimal. We anticipate high compliance with initial data collection as this is close to the time of patient registration. If any data is missing imputation will not be done.

Any problems with trial data will be queried with the Trial Managers, Data Managers, or statisticians, as appropriate. If possible, data queries will be resolved, although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. This will be minimised.

3.4 Data coding

The variable codings will be as specified on the CRF.

3.5 Management of datasets

Below is the standard policy for management of data in the CTU as given in the CTU SOPs.

At the time of final analysis:

The trial database will be stored in MACRO:

- In collaboration with the Statistician, the Data Manager will file out from MACRO a dataset of all data stored in the database. This will act as the frozen dataset. It is the responsibility of the statistician to accurately record the date of freezing and ensure all data is retrieved.
- If any outstanding data queries are resolved during the analysis that relate to data in the frozen dataset (e.g. problems that are found during analysis or amended CRFs that are returned to the CTU), the main MACRO database should be changed under the oversight of the Trial Data Manager.

4. DEFINITION OF TERMS

Give definition of any terms that require explanation.

Term	Definition
Best corrected distance visual acuity (BCVA)	Best corrected distance visual acuity will be obtained in both eyes by a trained optometrist using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts at baseline and at weeks 4, 8 and 12. If at week 12 the retina is dry, a further visit at week 16 will be undertaken and BCVA will be obtained at this visit. The EDTRS total score will be recorded and used for the analysis.
Central subfield retinal thickness	Central subfield retinal thickness (CST), as obtained in the central 1 mm area, will be determined by spectral domain optical coherence tomography (SD-OCT) and used for the analysis. In addition, presence or absence of intraretinal or subretinal fluid will be evaluated and recorded in the appropriate CRF. SD-OCT will be obtained in both eyes by an ophthalmic photographer at baseline and weeks 4, 8 and 12. If at week 12 the retina is dry, a further visit at week 16 will be undertaken and SD-OCT obtained at this visit.
Retinal perfusion	Retinal perfusion will be assessed by wide angle fundus fluorescein angiography (FFA). Wide-angle fluorescein angiographic images will be obtained by an ophthalmic photographer with the help of a research nurse at baseline and at the week 12 visit. The FFA run will be obtained from the study eye; images in the fellow eye will also be obtained at arterio-venous and later phases of the angiogram. Wide angle FFA results will be evaluated qualitatively for the presence/absence and extension of areas of retinal ischaemia. The FFA obtained at the 12 week follow up visit will be compared with that obtained at baseline to determine the existence of new areas of ischaemia and the increased/reduced size of pre-existing areas of ischaemia. In addition it is planned that areas of retinal ischaemia will also be detected and quantified automatically using an ImageJ program developed by our group. This software uses a combination of four binary masks, calculated independently, to adapt the detection of ischemic areas to different regions of the image. Images will be evaluated by an investigator masked to the participant and the study visit. Total area of ischaemia will be determined and used for the analysis.
Retinal sensitivity	Retinal sensitivity will be determined by macular microperimetry in both eyes. Microperimetry will be undertaken by an optometrist at baseline and at 12 weeks. If at week 12 the retina is dry, a further visit at week 16 will be undertaken and macular microperimetry obtained. Mean sensitivity in the central 10 degrees of the retina will be recorded and used for the analysis.
Schirmer test	The Schirmer test will be performed to measure tear production. The test will be undertaken by a Research Nurse at baseline and at week 12. If a further visit at week 16 is undertaken, this test will be also performed at this additional visit. This is a safe test which poses no risk to the patient. A negative test result is normal i.e. more than 10mm of moisture on the filter paper in 5 minutes. As both eyes normally secrete the same amount of tears, this test will be only done in the study eye (see Statistical Considerations section). This test will be done following completion of all functional tests (i.e. BCVA and microperimetry). This test is included as patients with DR

	often complain of dry eyes, most likely related to reduced corneal nerve fibre density. Given the effect of ARA 290 in increasing corneal nerve terminals observed in previous studies, we plan to evaluate whether tear film production may improve following this treatment. The millimetres of moisture on the filter paper for each eye will be recorded and used for the analysis
Patient reported outcomes	Patient reported outcomes will be evaluated by means of EQ-5D 5L and NEI VFQ-25 questionnaires which will be administered to patients at baseline and at week 12 (and at week 16 if applicable). The NEI VFQ-25 is a vision specific patient reported quality of life tool. This validated questionnaire has been used widely to evaluate visual outcomes in patients with eye diseases including DR. In addition to eliciting information about general health and vision it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision. This provides a comprehensive evaluation of vision related quality of life. A generic health status measure EQ-5D-5L will be used to generate utility data. Total scores will be recorded and used for the analysis. Suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) which will be administered to patients at baseline and weeks 4, 8 and 12. If at 12 weeks the retina is dry a further visit at week 16 will be arranged and questionnaires completed.
Blood/Urine Samples	A blood sample (34 mls (approximately 2 tablespoons)) and a urine sample will be taken at baseline, 12 weeks (and 16 weeks if the macular oedema resolved at week 12). The urine sample and part of the blood sample will be used to test for the following: • Pregnancy Test • Full blood cell count • CBC with reticulocytes • HbA1c • Glucose • Lipid profile (HDL, LDL, triglycerides) • C peptide levels • Creatinine clearance • Albumin excretion rate • Liver function test (ALT and AST)

5. SAMPLE SIZE CALCULATIONS

This will be an early phase, open label, interventional pilot study to evaluate the potential beneficial effect of ARA 290 for the treatment of patients with DR and DMO and further assess the safety of this treatment. Ten patients will be recruited. A sample of this size is expected to be sufficient to provide an indication of a potential beneficial effect of the drug on the outcomes investigated and further information on safety of ARA 290 in a diabetic population. Data obtained in this study will be used to inform future larger studies.

6. ANALYSIS PRINCIPLES

In participants in whom both eyes are eligible for inclusion into the study, the eye with the better BCVA will be used as the study eye; however data will be collected and evaluated for both eyes.

Descriptive statistics will be used for the evaluation of primary and secondary outcomes. Differences in mean (SD) change from baseline for all the continuous variables investigated including visual acuity, central subfield thickness, area of retinal ischaemia, retinal sensitivity, patient reported outcome scores as well as levels of ARA 290 antibodies. Confidence intervals will also be presented. When data is not normally distributed, median (interquartile range) will be presented.
Adverse events will be presented using counts and percentages. Additionally, the % of participants with 10 or more and 15 or more ETDRS letter gain will be also reported. Data obtained at week 16 would have been similarly evaluated; however no patients required a 16-week visit.

Exploratory analysis in relation to inflammatory markers and carbamylated and glycosylated albumin will also be observed from baseline to the week 12 visit.

If the retinal perfusion image analysis is not available, it may be presented in a later report.

Additional analysis (not specified in the protocol) will be performed to explore the treatment effect in the non-study eye for (a) those patients with DMO in the non-study eye that did not fulfil the criteria for inclusion into the study (e.g. in patients with central retinal subfield thickness of < 400 microns or in patients with non-central involving DMO) and (b) patients with DMO in the non-study eye that fulfilled criteria for inclusion into the study (e.g. ≥400 microns) .

As the analysis is only descriptive, no imputation or sensitivity analysis will be performed.

7. ANALYSIS DETAILS

The results of the analyses will be reported following the principle of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

7.1 Recruitment and follow-up patterns

- Recruitment by month
- The number of withdrawals

7.2 Baseline Characteristics

- Gender, n(%)
- Age(years), mean(sd)
- Weight(kg), mean(sd)
- Height(m), mean(sd)
- BMI(kg/m^2), mean(sd)
- Blood Pressure(mmHg), mean(sd) – systolic, diastolic
- Heart Rate(BPM), mean(sd)

- Temperature(degrees Celsius), mean(sd)
- Oxygen saturation(%), mean(sd)
- C peptide(pmol/L or nmol/L), mean(sd)
- HbA1C(mmol/L), mean(sd)
- Glucose(mmol/L), mean(sd)
- Type of diabetes, n(%)
- Liver Function Test, mean(sd)
- Triglycerides, mean(sd)
- Albumin creatinine ratio, mean(sd)
- HDL, mean(sd)
- LDL, mean(sd)
- Study Eye, n(%)
- Co-morbidities
- Ophthalmologic condition

7.3 Trial treatment

- Number of treatments administered
- Treatment compliance/tolerance including reasons for early discontinuation or protocol violations, n (%)
- Additional treatments given

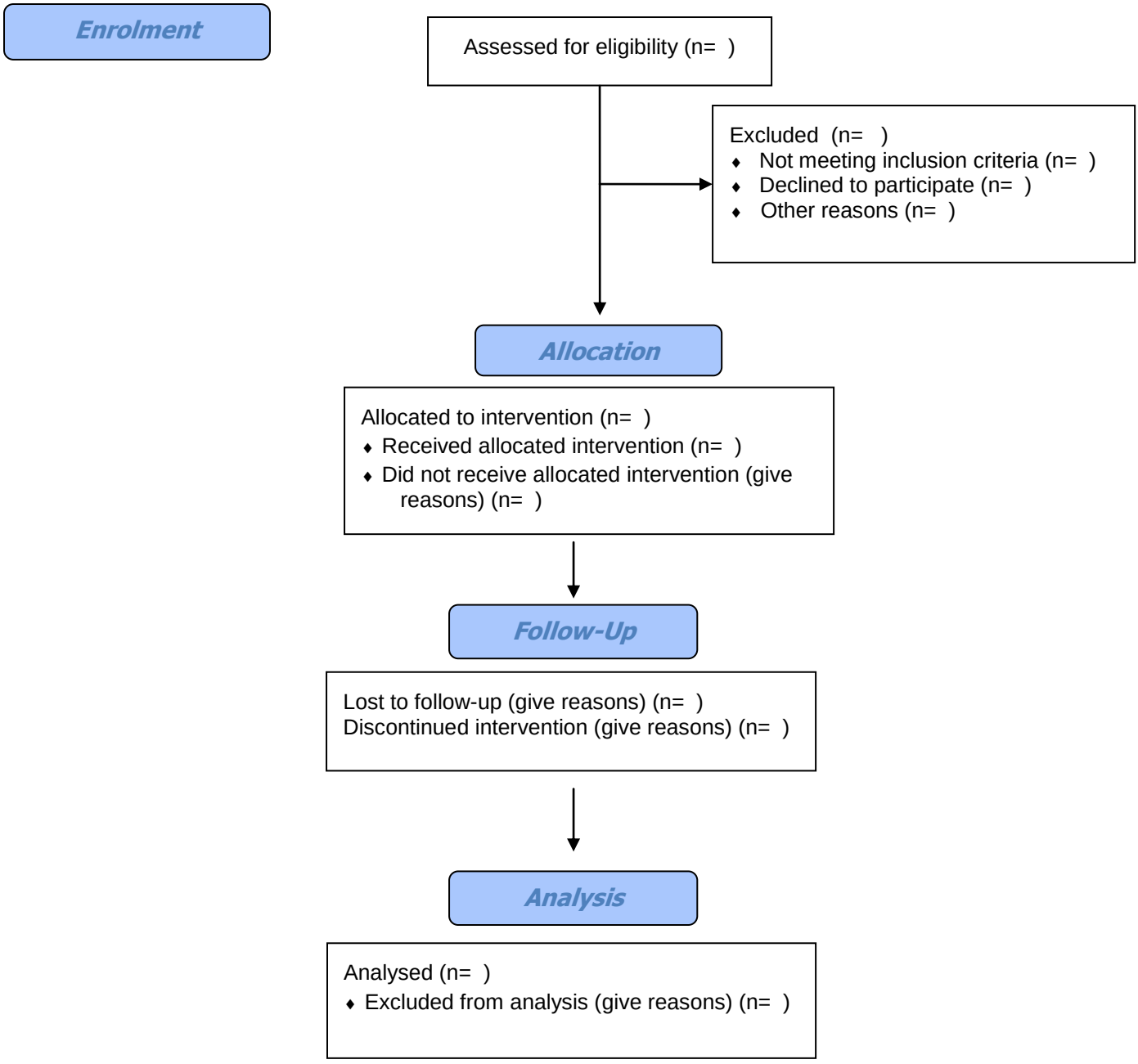
7.4 Trial events

- Change from baseline to week 12 in best corrected distance visual acuity, mean(sd)
- Change from baseline to week 12 in central subfield thickness, mean(sd)
- Change from baseline to week 12 in central retinal sensitivity, mean(sd)
- Change from baseline to week 12 in retinal perfusion, n(%)
- Change from baseline to week 12 Total area of ischaemia, mean (sd)
- Change from baseline to week 12 in tear production, mean(sd) (study eye only)
- Change from baseline to week 12 in patient reported outcomes, mean(sd)
- Change from baseline to week 12 in ARA 290 antibodies, mean(sd)
- Adverse events, n(%)
- % of participants with ≥10 ETDRS letter gain, n(%)
- % of participants with ≥15 ETDRS letter gain, n(%)
- Change from baseline to week 12 in inflammatory biomarkers, mean(sd)
- Change from baseline to week 12 in Carbamylated Albumin, mean(sd)
- Change from baseline to week 12 in Glycosylated Albumin, mean(sd)
- Change from baseline to week 12 in HbA1C, mean(sd)

7.5 Toxicity/ Symptoms

- Adverse Events (AEs), Serious adverse events (SAEs), related AEs and SAES, AEs and SAEs that led to study discontinuation, and Suspected unexpected serious adverse reactions (SUSARs)
- Mortality

7.6 CONSORT Flow Diagram



8. ADDITIONAL INFORMATION

8.1 Trial management group (TMG)

A Trial Management Group (TMG) will be established and Chaired by the CI. The TMG will have representation on it from the CTU and other investigators/collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician). This group will have responsibility for the day to day operational management of the trial, and regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

A TMG Charter will be drawn up to detail the terms of reference of the TMG including roles and responsibilities. A Trial Steering Committee (TSC) will not be established for the trial and therefore the TMG will oversee the progress of the trial in terms of its organisation and accrual with the aim of steering it towards its overall objectives and will report to the Sponsor/Funder.

8.2 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed comprised of one diabetologist (Prof. Tim Lyons), two ophthalmologists with expertise on DR and DMO (Dr Sobha Sivrapasad and Mr David Steel), and a Statistician (Dr Jonathan Cook) who is experienced in the analysis of clinical trials and will act as Chair for the DMEC. These members will be independent of the trial. A DMEC Charter will be drawn up to detail the terms of reference of the DMEC including roles and responsibilities. The DMEC's responsibility is to safeguard the interests of the trial participants, in particular with regard to safety, and to protect the validity and credibility of the trial. DMEC meetings will be formally minuted.

The inaugural meeting of the DMEC will take place prior to recruitment commencing. After recruitment commences the DMEC will review safety data at approximate 4 week intervals (with the first review commencing approximately 8 weeks after the first patient is recruited). The Chair of the DMEC will decide if these reviews raise any issues or concerns which require the DMEC to meet to discuss further. In addition, approximately every 3 months, the DMEC will review a full report on trial data (including outcome data, recruitment, pharmacovigilance and protocol deviations).

The DMEC will advise if in their view, the data arising from the study has provided 'proof beyond reasonable doubt' that for all, or some, the treatment should not be continued and standard treatment should be provided. Following a report from the DMEC, the CI will decide in consultation with the Sponsor what actions, if any, are required.
Membership of the DMEC will include:

Prof Jonathan Cook, (Chair), Associate Professor, Deputy Director of SITU, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology & Muscoloskeletal Sciences, University of Oxford, Botnar Research Centre, Nuffield Orthopaedic Centre, Windmill Road, OXFORD, OX3 7LD

Prof Tim Lyons, Chair of Diabetes and Translational Research, Institute of Clinical Sciences; Block A, Queen's University Belfast, Grosvenor Road, Belfast, BT12 6BA

Dr David Steel, Honorary Clinical Senior Lecturer, Institute of Genetic Medicine, Newcastle University
Dr Sobha Sivaprasad, Consultant Ophthalmologist, Moorfield Eye Hospital, 162 City Road, London, EC1V 2PD

9. SIGNATURES OF APPROVAL

Date:
Version:

This document has completed a final review and is understood and approved by the following:

NOEL COI		26/7/17
Chief investigator	*Chief Investigator signature*	Date dd/mm/yyyy
EVIE GARDNER	Evie Gardner	26/7/17
Trial Statistician	*Trial Statistician Signature*	Date dd/mm/yyyy

Appendix 1: Summary Tables

Table 1. Baseline and Week 12 Characteristics

Characteristics		ARA290-DMO n=<n>	Week 12 n=(%)
Gender	Male	n(%)	-
	Female	n(%)	-
Study Eye	Left	n(%)	-
	Right	n(%)	-
Type of diabetes	Type 1	n(%)	-
	Type 2	n(%)	-
Age (years)		xx.x ± xx.x	xx.x ± xx.x
Weight (kg)		xx.x ± xx.x	xx.x ± xx.x
Height (m)		xx.x ± xx.x	-
BMI (kg/m2)		xx.x ± xx.x	-
Systolic Blood pressure (mmHg)		xx.x ± xx.x	xx.x ± xx.x
Diastolic Blood Pressure		xx.x ± xx.x	xx.x ± xx.x
Heart rate (bpm)		xx.x ± xx.x	xx.x ± xx.x
Temperature (degrees celsius)		xx.x ± xx.x	xx.x ± xx.x
Oxygen saturation (%)		xx.x ± xx.x	xx.x ± xx.x
C peptide (ng/ml)		xx.x ± xx.x	xx.x ± xx.x
HbA1c (mmol/L)		xx.x ± xx.x	xx.x ± xx.x
Glucose (mmol/L)		xx.x ± xx.x	xx.x ± xx.x
HDL (mmol/L)		xx.x ± xx.x	xx.x ± xx.x
LDL (mmol/L)		xx.x ± xx.x	xx.x ± xx.x
Triglycerides (mmol/L)		xx.x ± xx.x	xx.x ± xx.x
Albumin Creatine Ratio		xx.x ± xx.x	xx.x ± xx.x
Liver Function Test (LFT)	AST(mmol/L)	xx.x ± xx.x	xx.x ± xx.x
	ALT(mmol/L)	xx.x ± xx.x	xx.x ± xx.x

Mean ±SD presented for continuous variables (or median [interquartile range] when appropriate) and no. (%) for all categorical variables.

Data listings for characteristics including co-morbidities and ophthalmologic condition will be included as an appendix in the final statistical report.

Table 2. Treatment after Trial Entry

Treatment after Trial Entry	ARA290-DMO n = (%)
Study drug given	n(%)
Number of doses administered*	xx.x ± xx.x
Reasons for early termination of study drug	
Adverse Event	n(%)
Serious Adverse Event	n(%)
Protocol Deviation	n(%)
Other	n(%)
Protocol violations:	
Eligibility	n(%)
Study Drug Administration	n(%)
Visit out of schedule	n(%)
Other	n(%)

*patients are expected to have received 120 doses over 120 days.

Table 3.1 Main Clinical Outcome variables

		Study Eye						Non-Study Eye					
		Baseline		Week 12		Change		Baseline		Week 12		Change	
		n = (%)		n = (%)		n = (%)		n = (%)		n = (%)		n = (%)	
Primary outcome; best corrected distance visual acuity		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central subfield thickness (microns)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central retinal sensitivity (dB)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Retinal perfusion	Macular Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Foveal Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Peripheral Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Total area of ischaemia	xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Tear production (mm)*		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		-		-		-	
Patient reported	EQ5d-5L	xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		-		-		-	
	VFQ-25	xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		-		-		-	

outcome scores C-SSR	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	-	-	-
% of participants with ≥ 10 ETDRS letter gain	-	-	n(%)	-	-	n(%)
% of participants with ≥ 15 ETDRS letter gain	-	-	n(%)	-	-	n(%)

*Study eye only
Mean ±SD presented for continuous variables (or median [interquartile range] when appropriate) and no. (%) for categorical variables.

Table 3.2 Descriptive Statistics for Serum for ARA 290 Antibodies

Status	Timepoint	Result	n =
Screening Status	Baseline	Negative	N (%)
		Potential Positive	N (%)
	Week 12	Negative	N (%)
		Potential Positive	N (%)
Confirmatory Status	Baseline	Not Applicable	N (%)
		Negative	N (%)
		Positive	N (%)
	Week 12	Not Applicable	N (%)
		Negative	N (%)
		Positive	N (%)

Table 3.3 Exploratory Analysis (Non-Study Eye subgroups)

		Non-Study Eye (Central subfield thickness <400 microns)						Non-Study Eye(Central subfield thickness ≥400 microns)					
		Baseline		Week 12		Change		Baseline		Week 12		Change	
		n = (%)		n = (%)		n = (%)		n = (%)		n = (%)		n = (%)	
Primary outcome; best corrected distance visual acuity		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central subfield thickness (microns)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central retinal sensitivity (dB)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Retinal perfusion	Macular Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Foveal Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Peripheral Ischameia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Total area of ischaemia	xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
% of participants with ≥ 10 ETDRS letter gain		-		-		n(%)		-		-		n(%)	

% of participants with ≥ 15 ETDRS letter gain	-	-	n(%)	-	-	n(%)

Mean ±SD presented for continuous variables (or median [interquartile range] when appropriate) and no. (%) for categorical variables.

Table 3.3 Exploratory Analysis (Non-Study Eye subgroups)

		Non-Study Eye (DMO Absent)					
		Baseline		Week 12		Change	
		n = (%)		n = (%)		n = (%)	
Primary outcome; best corrected distance visual acuity		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central subfield thickness (microns)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central retinal sensitivity (dB)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Retinal perfusion	Macular Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Foveal Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Peripheral Ischameia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Total area of ischaemia	xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
% of participants with ≥ 10 ETDRS letter gain		-		-		n(%)	
% of participants with ≥ 15 ETDRS letter gain		-		-		n(%)	

Mean ±SD presented for continuous variables (or median [interquartile range] when appropriate) and no. (%) for categorical variables.

Data listings for the visual outcomes will be included as an appendix in the final statistical report.

Table 3.4 Exploratory Analysis (All Eyes with DMO >400 Microns)

		All Eyes with DMO ≥ 400 Microns					
		Baseline		Week 12		Change	
		n = (%)		n = (%)		n = (%)	
Primary outcome; best corrected distance visual acuity		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central subfield thickness (microns)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Central retinal sensitivity (dB)		xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
Retinal perfusion	Macular Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Foveal Ischaemia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Peripheral Ischameia	Present Absent N/A	n(%) n(%) n(%)	Present Absent N/A	n(%) n(%) n(%)	Extension Reduction No change N/A	n(%) n(%) n(%) n(%)
	Total area of ischaemia	xx.x ± xx.x		xx.x ± xx.x		xx.x ± xx.x	
% of participants with ≥ 10 ETDRS letter gain		-		-		n(%)	
% of participants with ≥ 15 ETDRS letter gain		-		-		n(%)	

Table 4.1 Safety Outcomes

		ARA290 n=<n>
AEs, SAEs and SUSARs	Total number of Adverse Events (AEs)	n
	Number of patients experiencing an AE	n (%)
	Total number of Adverse Reactions (ARs)	n
	Total number of Serious Adverse Events (SAEs)	n
	Number of patients experiencing an SAE	n (%)
	Total number of Serious Adverse Reactions (SARs)	n
	Total number of events related to study drug and unexpected (SUSARs)	n
	Total number of Deaths	n (%)
AE	General disorders and administration site conditions	n (%)
	Vascular disorders	n (%)
	Eye disorders	n (%)
	Gastrointestinal disorders	n (%)
	Psychiatric disorders	n (%)
	Metabolism and nutrition disorders	n (%)
	Infections and infestations	n (%)
	Nervous system disorders	n (%)
	Musculoskeletal and connective tissue disorders	n (%)
	Injury, poisoning and procedural complications	n (%)
	Respiratory, thoracic and mediastinal disorders	n (%)
	Skin and subcutaneous tissue disorders	n (%)
	Immune system disorders	n (%)
	Renal and urinary disorders	n (%)
	Cardiac disorders	n (%)
	Ear and labyrinth disorders	n (%)
	Investigations	n (%)
SAE	General disorders and administration site conditions	n (%)
	Vascular disorders	n (%)
	Eye disorders	n (%)
	Gastrointestinal disorders	n (%)
	Psychiatric disorders	n (%)
	Metabolism and nutrition disorders	n (%)
	Infections and infestations	n (%)
	Nervous system disorders	n (%)
	Musculoskeletal and connective tissue disorders	n (%)
	Injury, poisoning and procedural complications	n (%)
	Respiratory, thoracic and mediastinal disorders	n (%)
	Skin and subcutaneous tissue disorders	n (%)
	Immune system disorders	n (%)
	Renal and urinary disorders	n (%)
	Cardiac disorders	n (%)
	Ear and labyrinth disorders	n (%)
	Investigations	n (%)

Table 4.2 Adverse event summary of system organ class & preferred term

System Organ Class / Preferred Term		Total	Adverse Reaction (AR)	Unexpected Adverse Reaction (UAR)
Patients reporting at least one adverse event		n(%)	n(%)	n(%)
General disorders and administrative site conditions		n(%)	n(%)	n(%)
	Head Cold	n(%)	n(%)	n(%)
	Headache	n(%)	n(%)	n(%)
	Flu Symptoms	n(%)	n(%)	n(%)
	Non-cardiac Chest Pain	n(%)	n(%)	n(%)
Vascular disorders		n(%)	n(%)	n(%)
	Hypertension	n(%)	n(%)	n(%)
Eye disorders		n(%)	n(%)	n(%)
	Drop in visual acuity	n(%)	n(%)	n(%)
	Flashing lights	n(%)	n(%)	n(%)
Gastrointestinal disorders		n(%)	n(%)	n(%)
	Nausea	n(%)	n(%)	n(%)
	Diarrhoea	n(%)	n(%)	n(%)
	Vomiting	n(%)	n(%)	n(%)
Psychiatric disorders		n(%)	n(%)	n(%)
	Insomnia	n(%)	n(%)	n(%)
Metabolism and nutrition disorders		n(%)	n(%)	n(%)
	Hypertriglyceridemia	n(%)	n(%)	n(%)
	Hyperglycemia	n(%)	n(%)	n(%)
	Metabolism and nutrition disorders - other	n(%)	n(%)	n(%)
Infections and infestations		n(%)	n(%)	n(%)
	Infections – 'Other'	n(%)	n(%)	n(%)
Skin and subcutaneous tissue disorders		n(%)	n(%)	n(%)
	Facial Sunburn	n(%)	n(%)	n(%)
Investigations		n(%)	n(%)	n(%)
	GGT Increased	n(%)	n(%)	n(%)
	Abnormal blood test results	n(%)	n(%)	n(%)

Data listings for adverse events will be included as an appendix in the final statistical report.

Table 5. Exploratory Analysis – change from baseline to 12 weeks

Exploratory Analysis	Baseline	Week 12	Change
	n=(%)	n=(%)	n=(%)
Inflammatory Markers *			
Adenosine Deaminase (ADA)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Artemin (ARTN)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Axin-1 (AXIN1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Beta-nerve growth factor (BDNF)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Caspase 8 (CASP-8)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-C motif chemokine 4 (CCL4)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-C motif chemokine 19 (CCL19)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-C motif chemokine 20 (CCL20)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-C motif chemokine 25 (CCL25)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-C motif chemokine 28 (CCL28)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
CD40L receptor (CD40)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
CUB domain-containing protein 1 (CDCP1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-X-C motif chemokine 1 (CXCL1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-X-C motif chemokine 5 (CXCL5)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-X-C motif chemokine 6 (CXCL6)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-X-C motif chemokine 9 (CXCL9)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-X-C motif chemokine 10 (CXCL10)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-X-C motif chemokine 11 (CXCL11)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Cystatin D (CST5)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Delta and Notch-like epidermal growth factor-related recep (DNER)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Eotaxin-1 (CCL11)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Fibroblast growth factor 5 (FGF-5)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Fibroblast growth factor 19 (FGF-19)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Fibroblast growth factor 21 (FGF-21)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Fibroblast growth factor 23 (FGF-23)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Fms-related tyrosine kinase 3 ligand (Flt3L)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Fractalkine (CX3CL1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Glial cell line-derived neurotrophic factor (hGDNF)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Hepatocyte growth factor (HGF)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interferon gamma (IFN-gamma)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-1 alpha (IL-1 alpha)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-2 (IL-2)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-2 receptor subunit beta (IL-2RB)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-4 (IL-4)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-5 (IL-5)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-6 (IL-6)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-7 (IL-7)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-8 (IL-8)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-10 (IL-10)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-10 receptor subunit alpha (IL-10RA)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-10 receptor subunit beta (IL-10RB)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-12 subunit beta (IL-12B)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-13 (IL-13)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
interleukin-15 receptor subunit alpha (IL-15RA)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-17A (IL-17A)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-17C (IL-17C)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-20 (IL-20)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-20 receptor subunit alpha (IL-20RA)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x

Interleukin-22 receptor subunit alpha-1 (IL-22 RA1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-23 (IL-24)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Interleukin-33 (IL-33)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Latency-associated peptide transforming growth factor beta 1 (LAP TGF-beta-1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Leukemia inhibitory factor receptor (LIF-R)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Macrophage colony-stimulating factor 1 (CSF-1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Macrophage inflammatory protein 1-alpha (MIP-1 alpha)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Matrix metalloproteinase-1 (MMP-1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Matrix metalloproteinase-10 (MMP-10)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Monocyte chemotactic protein 1 (MCP-1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Monocyte chemotactic protein 2 (MCP-2)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Monocyte chemotactic protein 3 (MCP-3)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Monocyte chemotactic protein 4 (MCP-4)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Natural killer cell receptor 2B4 (CD244)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Neurotrophin-3 (NT-3)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Neurturin (NRTN)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Oncostatin-M (OSM)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Osteoprotegerin (OPG)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Programmed cell death 1 ligand 1 (PD-L1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Protein S100-A12 (EN-RAGE)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Signaling lymphocytic activation molecule (SLAMF1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
SIR2-like protein 2 (SIRT2)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
STAM-binding protein (STAMPB)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Stem cell factor (SCF)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Sulfotransferase 1A1 (ST1A1)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
T-cell surface glycoprotein CD5 (CD5)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
T cell surface glycoprotein CD6 isoform (CD6)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Thymic stromal lymphopoietin (TSLP)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
TNF-beta (TNFB)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
TNF-related activation-induced cytokine (TRANCE)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
TNF-related apoptosis-inducing ligand (TRAIL)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Transforming growth factor alpha (TGF-alpha)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Tumor necrosis factor (ligand) superfamily, member 12 (TWEAK)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Tumor necrosis factor (TNF)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Tumor necrosis factor ligand superfamily member 14 (TNFSF14)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Tumor necrosis factor ligand superfamily member 9 (TNFSF9)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Urokinase-type plasminogen activator (uPA)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Vascular endothelial growth factor A (VEGF-A)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Carbamylated Albumin	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Glycosylated Albumin	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
HbA1c (mmol/L)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x

*pg/mL

Mean ±SD presented (or median [interquartile range] when appropriate)