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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Ethics Reference Number:	15/NI/0197
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PROTOCOL AUTHORISATION

Protocol Title	A phase II Clinical Trial on the use of ARA 290 for the treatment of diabetic macular oedema
Protocol Acronym (if applicable)	ARA 290-DMO
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A review of the protocol has been completed and is understood and approved by the following:

NOEL LOI — Chief Investigator Name — Signature — Date: 13 / 9 / 2017 (DD / MM / YYYY)

EVIE GARDNER — Statistician — Signature — Date: 14 / 8 / 2017 (DD / MM / YYYY)

MICHAEL BRINES — Araim Pharmaceuticals representative — Signature — Date: 01/08/2017 (DD / MM / YYYY)

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Full Wording
AE	Adverse Event
anti-VEGF	Anti-Vascular Endothelial Growth Factor
AR	Adverse Reaction
ARA 290	Study drug
BCVA	Best Corrected Visual Acuity
BHSCT	Belfast Health & Social Care Trust
BMI	Body Mass Index
BRB	Blood Retinal Barrier
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CST	Central Subfield Retinal Thickness
CTA	Clinical Trial Authorisations
CTU	Clinical Trials Unit
DM	Diabetes Mellitus
DMEC	Data Monitoring And Ethics Committee
DMO	Diabetic Macular Oedema
DR	Diabetic Retinopathy
DSUR	Development Safety Update Report
EPO	Erythropoietin
EQ-5D 5L	Generic Health Status Measure
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FFA	Fundus Fluorescein Angiography
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference Of Harmonisation
IMP	Investigational Medicinal Product
IRR	Innate Repair Receptor
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IMPD	Investigational Medicinal Product Dossier
MHRA	Medicine And Healthcare Products Regulatory Agency
NEI VFQ-25	Vision Specific Patient Reported Quality Of Life Tool
NHS	National Health Service
NICTU	Northern Ireland Clinical Trials Unit
PDR	Proliferative Diabetic Retinopathy
PI	Principal Investigator
PIS	Patient Information Sheet
QUB	Queen's University Belfast
REC	Research Ethics Committee
R & D	Research & Development
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Spectral Domain
SD-OCT	Spectral Domain Optical Coherence Tomography
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VEGF	Vascular Endothelial Growth Factor

1 STUDY SUMMARY

Scientific title	A Phase II Clinical Trial on the use of ARA 290 for the treatment of diabetic macular oedema (ARA 290-DMO)
Public title	A Phase II Clinical Trial on the use of ARA 290 for the treatment of diabetic macular oedema (ARA 290-DMO)
Health condition(s) or problem(s) studied	Diabetic macular oedema (DMO)
Study Design	A prospective, open label, interventional, single centre, investigator led, phase II study to examine the effect of ARA 290 on diabetic macular oedema in patients with type 1 or 2 diabetes.
Study Aim and Objectives	**Primary Objective**: The aim or primary objective of the study is to determine whether ARA 290 administered at a daily dose of 4mg subcutaneously for 12 weeks to patients with diabetes mellitus (DM) and DMO will have a beneficial effect on mean change in best corrected visual acuity (BCVA) from baseline values to week 12. **Secondary Objectives**: 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 $\geq$ 10 and $\geq$ 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 ARA 290 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.
Study Intervention	Subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks
Primary Outcome	Change from baseline to week 12 (+/– 7 days) in best corrected distance visual acuity
Key Secondary Outcomes	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 7. Adverse events

	% of participants with ≥ 10 ETDRS letter gain % of participants with ≥ 15 ETDRS letter gain
Exploratory Outcomes	Changes from baseline to week 12 (+/– 7 days) in: 1. Inflammatory markers 2. Carbamylated and glycosylated albumin
Key Inclusion and Exclusion 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
Countries of Recruitment	United Kingdom
Study Setting	Secondary care hospital setting
Target Sample Size	10 patients
Study Duration	15 months

2 STUDY TEAM

Chief Investigator (and Local Principal Investigator)	**Professor Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queens University Belfast 97 Lisburn Road BT9 7BL
Co-Investigators	**Dr David Armstrong** Academic Clinical Lecturer The Wellcome-Wolfson Institute for Experimental Medicine Queens University Belfast 97 Lisburn Road BT9 7BL
Statistician	**Evie Gardner** Senior Biostatistician Northern Ireland Clinical Trials Unit (NICTU) 1st Floor Elliott Dynes Building Royal Hospitals Grosvenor Road Belfast Northern Ireland, BT12 6BA
Clinical Trials Unit	**Northern Ireland Clinical Trials Unit (NICTU)** 1st Floor Elliott Dynes Building, The Royal Hospitals Grosvenor Road, Belfast, Northern Ireland, BT12 6BA
Contact for public queries	**Northern Ireland Clinical Trials Unit (NICTU)** 1st Floor Elliott Dynes Building. The Royal Hospitals Grosvenor Road Belfast, BT12 6BA Tel: 028 9063 5794 Email: info@nictu.hscni.net
Contact for scientific queries	**Professor Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queens University Belfast 97 Lisburn Road BT9 7BL Tel: 028 90 976462 Email: n.lois@qub.ac.uk **Nuala Jane Lavery** Research Nurse The Wellcome-Wolfson Institute for Experimental Medicine Queens University Belfast 97 Lisburn Road BT9 7BL Tel: 028 90 976465 Email: n.lavery@qub.ac.uk

3. BACKGROUND AND RATIONALE

Diabetic Retinopathy (DR) is the most common microvascular complication of Diabetes Mellitus (DM) and a leading cause of visual loss among individuals of working age [1, 2]. Patients with DR may irreversibly lose sight as a result of the development of Diabetic Macular Oedema (DMO), which represents the accumulation of fluid in the central part of the retina, the macula, responsible for detailed central vision.

3.1 Background Information

A recently conducted individual participant data meta-analysis, which included 22,896 individuals from 35 studies conducted in Asia, Australia, Europe, and US, provided an overall age-standardised prevalence of DMO of 6.81% [3]. Based on this, it could be conservatively estimated that there are ~220,000 people in UK affected by DMO (*http://www.diabetes.org.uk/About_us/What-we-say/Statistics/Diabetes-prevalence-2012*). Due to the increasing numbers of people with DM, principally the type 2 form of the disease, predominantly a result of the increased overweight and obesity of the population, it is expected that the burden of DR and DMO will continue to rise.

Patients with DMO can be treated with focal or grid macular laser or, most commonly, with injections into the eye of anti-Vascular Endothelial Growth Factor (anti-VEGF) drugs. Once treated, patients are followed long-term to determine whether DMO recurs. Following anti-VEGF treatment, patients need to be followed monthly or bi-monthly during the first year of treatment and every three-four months thereafter [4-6] as the DMO can recur. Taking this into account, there would be between 986,476 and 1,972,953 visits generated during the first year of treatment for all patients with DMO in UK and ~876,868 visits if all patients were to remain stable thereafter (it could be conservatively estimated that around 80% would reactivate [4] which would increase the number of visits considerably).

Patients with DMO are evaluated by slit-lamp biomicroscopy, spectral domain (SD) optical coherence tomography (SD-OCT) and, if required, fundus fluorescein angiography (FFA). SD-OCT allows determining the presence and location within the retina of fluid in DMO and obtaining measures of the macular thickness, which allows the evaluation of the treatment response. FFA may be obtained to determine the presence and extension of areas of retinal ischaemia.

3.2 Rationale for the Study

Given the high number of people with DMO, the need for patients to be seen at short follow-up intervals and the need for frequent treatments as well as the imaging technologies required for the evaluation of these patients the workload related to DMO is making it impossible for health care services to cope with the demand. Furthermore, around 40-50% of people with DMO do not respond to anti-VEGF treatment [4]. As one year outcomes (and at subsequent time points) cannot be predicted by the response to the first few treatments with anti-VEGF [7], most people require a year of treatment before they can be considered truly “non-responders”. Although infrequent, complications of intravitreal injections can occur, including increased intraocular pressure, cataract, retinal detachment and endophthalmitis. For the above reasons, new effective therapeutic modalities for DMO that may require less intensive regimes and/or alternative routes of administration (rather than injections into the eye) are very much needed.

3.3 Rational for the Intervention

The pathogenesis of diabetic retinopathy and DMO is complex; inflammation is recognised to play a key role in the series of events that lead to the occurrence and persistence of this sight threatening complication of diabetic retinopathy. Thus, it has been established that early on in the course of the disease there is interaction between circulating immune cells (e.g. monocytes, neutrophils) and the retinal vasculature which begins with leukostasis, which is

accepted as contributory to occlusion, breakdown of the blood retinal barrier (BRB) and subsequent oedema, and degenerative vascular pathology in diabetic retinopathy [8]. Neutrophils and monocytes/macrophages are the major source of pro-inflammatory cytokines, including Vascular Endothelial Growth Factor (VEGF) [9-11]. The increased released of cytokines by inflammatory cells would lead to tissue injury and cell loss [11].

ARA 290 is a synthetic peptide, analogue of erythropoietin (EPO), with marked anti-apoptotic and anti-inflammatory effects [12, 13]. Unlike EPO, ARA 290 is not haematopoietic and, subsequently, is free of the possible side effects linked to EPO such as thrombotic events, which can be life threatening. Given the anti-inflammatory and anti-apoptotic effects of ARA 290 [14, 15], it is possible that this peptide could have a beneficial effect on the treatment of DMO and, thus, warrants investigation [16]. Moreover, ARA 290 protected against retinal blood vessel and neuroglial degeneration and reduced leakage from blood vessels into the retina in an experimental model of diabetic retinopathy [17].

No adverse pharmacologic or toxicologic effects of ARA 290 were identified in general toxicology studies in rats and rabbits after daily subcutaneous administration of up to 6 months duration in rats and 9 months duration in rabbits at maximum doses/concentrations of at least 100 – 1000 fold the initial anticipated minimal effective human dose of 1 microgram/Kg body weight (body surface area adjusted) or the theoretical maximum plasma concentration following bolus administration to the plasma compartment, in standard safety pharmacology battery for central nervous system, respiratory and electrocardiogram effects nor in in-vitro and in-vivo genotoxicity studies [18].

Similarly, the first in human studies comprising intravenous administration of a single ascending dose and multiple ascending dose in healthy volunteers, single intravenous and subcutaneous cross-over study in healthy volunteers and in subjects with renal impairment, and intravenous repeat dose in end-stage renal disease subjects undergoing haemodyalisis raised no safety concerns. Furthermore, studies using intravenous and subcutaneous administration of ARA 290 to patients with sarcoidosis [19, 20] and type 2 diabetes mellitus [21], including studies using the same dose and route as that proposed in the current study (4 mg subcutaneous administration of ARA 290), as well as studies in patients with critical limb ischaemia, and rheumatoid arthritis have supported further the safety profile of ARA 290. No allergic reactions have been observed to ARA 290.

Specifically, two studies have been previously conducted in people with type 2 diabetes mellitus, pre-diabetes and/or drug-naïve type 2 diabetes. In both, a daily subcutaneous 4 mg dose of ARA 290 administered during a 4 week period was used. In these studies 24 and 12 patients, respectively, received ARA 290 (24 and 12 received placebo, respectively). At the dosage used, ARA 290 appeared to be safe. Adverse events were generally mild; the most common being gastrointestinal issues, sleep disturbance and headache; the frequency of adverse events was similar in both ARA 290 and placebo groups.

The dose and route of 4 mg was chosen for the current study as pharmacokinetic studies using ARA 290 demonstrated that a daily subcutaneous dose of 4 or 6 mg of ARA 290 resulted in consistent blood levels above 1-2 nM, the minimum projected exposure for efficacy [18]. The current phase 2 study however, entails for the first time prolonging the duration of treatment, from 28 days, as used in most previous studies, to 84 days. The three month duration of the ARA 290 dosage was chosen as it is expected that if treatment were to be beneficial, functional and anatomical improvements could potentially be detected in this time period but may not be seen earlier, as only patients with severe DMO (central retinal thickness of $\geq$ 400 microns) will be included in this investigation. Furthermore, it is unlikely that a detrimental effect on vision will be observed by postponing anti-VEGF treatment for this length of time [22]

Patients with DMO and thick retinas (> 400 microns) naïve to treatment will be included. It is unlikely that on these, spontaneous resolution of the macular oedema would occur during a 3-month period and thus, if improvement or resolution is observed during the study it could most

likely be attributed to the treatment with ARA 290. It was decided to include treatment naïve patients rather that people that had previously failed to respond to current standard treatment (anti-VEGF) because currently it is not possible to determine treatment failure due to anti-VEGF therapies unless treatment has been undertaken for many months, likely for a minimum of a year [23, 24]. Thus, it would be difficult to determine, if no benefit were to be observed after ARA 290 administration in this potential group, whether it was due to a lack of a treatment effect or whether it could relate to chronic and irreversible damage that may have taken place.

1. STUDY AIMS AND OBJECTIVES

4.1 Research Hypothesis

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.

4.2 Study Aim

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 DMO, 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.

4.3 Study Objectives

4.3.1 Primary Objective:

To determine whether ARA 290 has a beneficial effect on BCVA in people with DM and DMO.

4.3.2 Secondary Objectives:

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 $\geq$ 10 and $\geq$ 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.

4.4 Exploratory Outcomes

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.

5. STUDY DESIGN

5.1 Study Design

A prospective, open label, interventional, single centre, investigator led, phase II study to examine the effect of ARA 290 on diabetic macular oedema in patients with type 1 or 2 diabetes.

5.2 Study Schematic Diagram

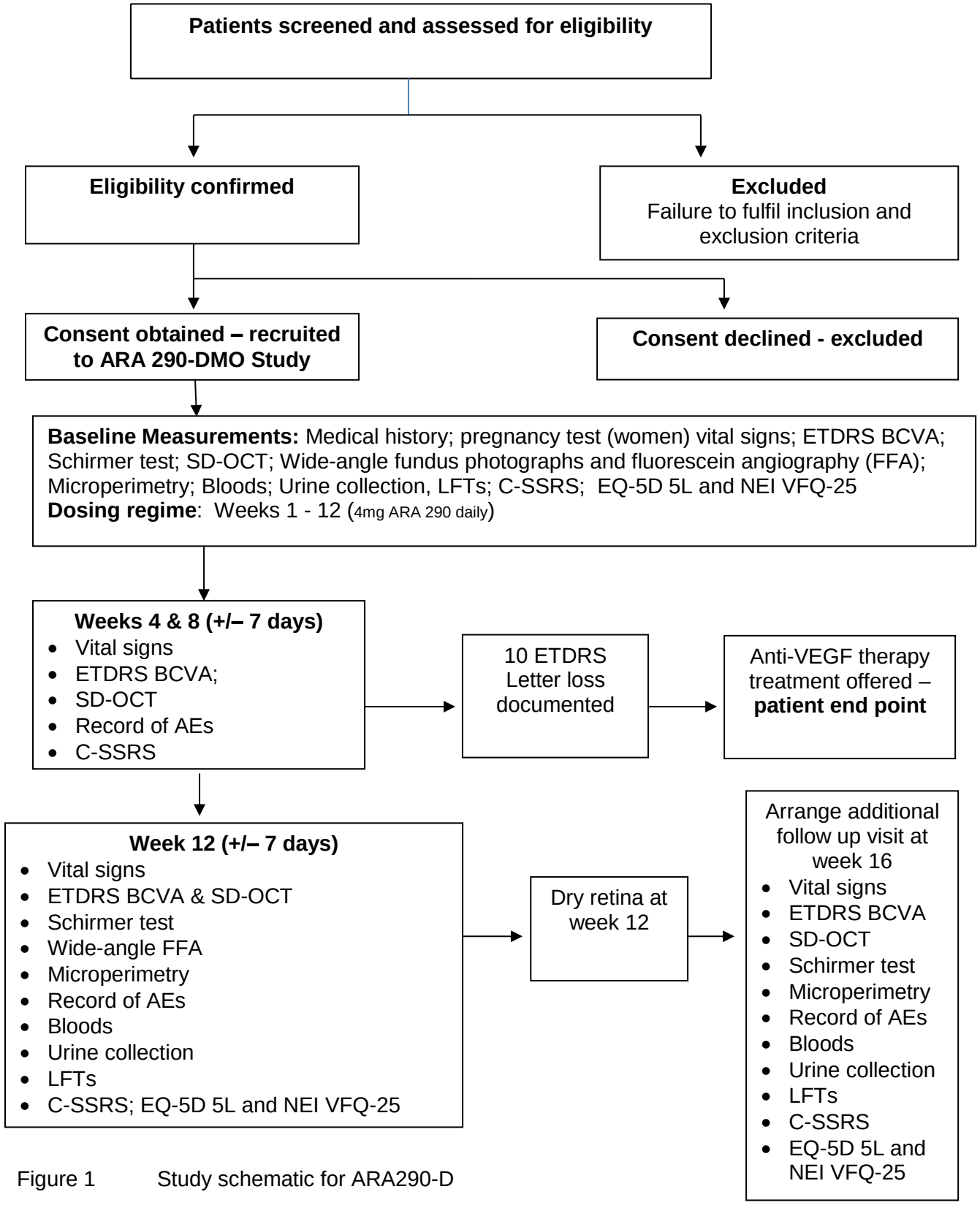

Figure 1 Study schematic for ARA290-D

5.3 Study Timeline

Table 1: Study Timeline Gantt Chart

Year	**1**				**2**
Quarter	**1**	**2**	**3**	**4**	**1**
Project - months	**3**	**6**	**9**	**12**	**15**
Trial Stage	**Set up**	**Main Trial**	**Main Trial**	**Main Trial**	**Reporting**
Trial Set-up	x	x			
Recruit Staff	x	x			
Protocol Development	x				
Ethics/Regulatory Approvals	x	x			
R&D Approvals	x	x			
Site Initiation/Training		x			
Patient Recruitment		x	x		
Patient Treatment/Follow Up		x	x	x	
Data Collection (including questionnaires)		x	x	x	
Trial Management Meetings	xxx	xxx	xxx	xxx	xxx
DMEC	x	x	x	x	x
Trial Close Out (sites)					x
Data Analysis					x
Trial Report					x
Dissemination					x

The study will run for 15 months with a planned study timeline as follows:

Months 1-3: Protocol finalised. MHRA, Ethics and Governance approvals sought

Months 4-9: Recruitment of 10 patients

Month 13: Follow-up completed in all patients recruited

Months 14-15: Data analysis and manuscript(s) preparation

5.4 End of Study

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.

6. OUTCOME MEASURES

6.1 Primary Outcome Measure

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

6.2 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
7. Adverse events

% of participants with ≧ 10 ETDRS letter gain
% of participants with ≧ 15 ETDRS letter gain

6.3 Exploratory Outcome

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

1. Inflammatory markers
2. Carbamylated and glycosylated albumin

7. STUDY SETTING & PATIENT ELIGIBILITY

7.1 Study Setting

Secondary care: Patients will be recruited from the Belfast Health & Social Care Trust (BHSCT).

7.2 Study Centre Requirements

To undertake the study assessments required the following equipment must be available at the participating centre:

- ETDRS Visual Acuity Charts
- Heidelberg Spectralis System
- Microperimetry Equipment
- Optos Wide-field Retinal Imaging

All equipment provided and used in the study must be maintained and calibrated. Trial specific procedures relating to the use of the above equipment will be provided with the trial training manual. The PI will be responsible for ensuring that all study staff using this equipment are fully trained in these SOPs and all training is fully documented.

7.3 Eligibility Criteria

Eligibility to participate in the trial will be confirmed by the PI who is a medically qualified doctor, an ophthalmologist and a retinal specialist. The PI will annotate the patient's medical notes to confirm that the patient has met the eligibility criteria for the study.

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

7.3.1 Inclusion criteria:

1. Patients with DR 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.

7.3.2 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 systemic or topical 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
12. Active proliferative diabetic retinopathy (PDR) requiring treatment.
13. Patients with other eye diseases besides DR
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.

7.4 Co-enrolment Guidelines

Patients currently enrolled in other investigational drug studies are not eligible to participate. Patients enrolled in other observational studies are potential candidates for this study.

7.5 Allocation Concealment Mechanism

This will be an open label study thus the Principal Investigator (PI) and patients will not be masked to study treatment.

8. PATIENT SCREENING & CONSENT

8.1 Recruitment & Retention

The ARA 290-DMO study will recruit 10 patients. The PI or designee will telephone all trial participants prior to their scheduled visits, to remind them of the visit to encourage participation and retention.

8.2 Screening Procedure

Patients attending ophthalmology clinics at the Belfast Health and Social Care Trust will be prospectively screened by the PI or designee based on the inclusion/exclusion criteria as specified in the protocol. Prospective patients will be provided with a REC approved Patient Information Sheet (PIS) to take home with them to allow them adequate time to review the PIS and note any questions on participation in the study. The PI or designee will carry out a follow up telephone call with the patient to ascertain their willingness to participate in the study. If the patient is willing to participate they will be invited to attend a more detailed face to face screening/baseline visit to confirm their eligibility and gain their written consent.

Patients may also be identified as possible eligible candidates for the study based on their referral to ophthalmology clinics and/or review by other ophthalmology consultants. In this case, patients may be contacted by the PI by phone and asked, following an explanation about the study, whether they would like to receive further information by post about the study. If the patient is in agreement, a Patient Information Sheet will be sent to them by post, followed up by a phone call 1 week later, to ask them if they would consider participating in the study. If their response is affirmative, they will be given an appointment to come to the clinic for a more detailed face to face screening/baseline visit.

At the screening/baseline visit a member of the study team will discuss the study with the patient in full to determine their interest in participating and will answer any queries or concerns the patient may have. If the patient is willing to proceed, written consent will be obtained.

The Clinical Trials Unit (CTU) will provide screening logs which must be completed by the PI or designee to document all patients screened for the study and all patients recruited. Patients screened and not recruited on to the study should also be documented on the screening log, including the reason for not being enrolled on the study. The PI or designee will be required to submit screening logs to the CTU approximately every 2 months.

8.3 Informed Consent Procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible patients may only be included in the trial after written informed consent is obtained. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be documented in the patient's medical records (source documents will be reviewed at the time of on-site monitoring visits).

Informed Consent Forms (ICF) approved by the REC will be provided by the CTU. The PI or designee is responsible for ensuring that informed consent for trial participation is given by each patient prior to any trial treatment being administered. This requires that the ICF be signed and personally dated by the patient prior to any trial treatment proceeding. If no consent is given a patient cannot be recruited into the trial.

The CTU will provide patient information sheets (PIS) approved by the REC. The PI or designee is responsible for ensuring that all patients are given a copy of the PIS and are allowed adequate time to review this and the opportunity to ask any study related questions. All patients should have the capacity to self-consent; this should be judged by the PI or the designated member of the study team who will have the responsibility for taking consent. Two copies of the ICF must be signed and personally dated by the patient and the individual taking

consent. A copy of the signed ICF will be filed in the patient's medical records, whilst the originals will be retained by the patient and by the PI in the Investigator Site File (ISF).

The patient's medical notes will be annotated by the PI to confirm that the patient has given written consent and has been recruited onto the study.

Following the recruitment of a patient onto the study, the PI or designee will issue a letter to the patient's General Practitioner (GP) to inform them that their patient is participating in the ARA 290-DMO trial. The patient will be advised of this contact with their GP on the PIS.

8.4 Withdrawal of Consent

Patients may withdraw or be withdrawn from the trial at any time without prejudice. In the event of consent withdrawal, patients will be asked for their permission to use the data already collected to date. If this permission is declined, then any data collected to date on that patient will not be entered into the trial analysis.

If the patient and/or PI request termination of the trial drug during the treatment period, the drug will be stopped and the patient will revert to standard care treatment. The patient will be advised that if any event occurs within 28 days of receiving the last dose of the study drug, which the patient considers might be related to the study drug, the patient should contact the clinic to discuss with the PI.
As an additional safeguard, the PI or designee will contact the patient by telephone 4 weeks post study drug termination to assess if the patient has experienced any adverse events.

If a patient withdraws or is withdrawn from the trial they will be offered the standard care treatment which is currently anti VEGF drugs within the National Health Service (NHS).

Withdrawal of consent, or patient/PI request to terminate the study drug, will be recorded on the Case Report Form (CRF).

9. STUDY DRUG

9.1 Study Drug Description

ARA 290 is an 11-amino acid peptide derived from the spatial configuration of the external face of helix B of the protein erythropoietin. ARA 290 is a novel, first-in-class activator-peptide of the Innate Repair Receptor (IRR) that antagonises inflammation and tissue injury and promotes endogenous repair mechanisms. ARA 290 is an anti-inflammatory agent that has an effect in preventing the death of cells. As inflammation is known to play a role in the occurrence of DMO it could potentially be helpful in treating patients with this condition. The ARA 290 drug product used for subcutaneous injection is provided as aseptic vials containing 5.6 mg ARA 290, which after reconstitution with 0.66 mL sterile Water for Injection, contains a solution of 8 mg/mL ARA 290 in a 20 mM sodium phosphate buffer, pH 6.5, containing 1% sucrose and 4% D-mannitol. A volume of 0.5 mL contains 4 mg ARA 290.

9.2 Study Drug Supply

As described in the IMPD, Patheon Italia S.P.A. 2o Trav. SX via Morolense, 5 03013 – Ferentino, Italy and PCI, Biotec House, Western Avenue, Bridgend Industrial Estate, Bridgend, CF31 3RT are responsible for manufacture, QP release, import and shipment of ARA290.

Study drug packs will be packaged and labelled by Victoria Pharmaceuticals, Plenum Building, Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA in compliance with applicable regulatory requirements.

Study drug packs will be dispatched to the responsible pharmacist at the participating site under the instruction of the Trial Manager.

Each patient will be given an initial pack containing 30 vials of study drug. Replacement packs of 30 vials will be provided at visits as required, to a maximum of 3 packs x 30 vials.
Each pack will provide enough study drug for 28 days treatment (with 2 days of study drug overage to allow for the drug spilling or spoiling, and to provide a +/- 2 day window around study visits).

9.3 Study Drug Accountability

The hospital pharmacy will maintain accurate records of all Investigational Medicinal Product (IMP) received (including date of receipt, batch numbers, expiry date, quantities of drug shipments), dispensed and returned on the Drug Accountability Log. Records must be available to the study monitors on request. Patients will be asked to return used and unused vials of study drug to the site at each study visit as applicable. Unallocated, unused and used study drug will be destroyed at site with permission from the CTU and in accordance with site pharmacy procedure for destruction of IMP and hospital waste management policies. A record of the destruction will be maintained.

9.4 Study Drug Storage

The study drug will be stored in BHSCT Pharmacy under refrigerated conditions at 2-8°C When a study pack is dispensed to a patient, the patient will be advised to store this in their home refrigerator.

9.5 Study Drug Administration

After giving consent and being recruited on to the study, the patient's baseline assessment will be carried out and recorded.

The first subcutaneous injection of ARA 290 at a dose of 4 mg will be self-administered by the patient at the first patient visit. The patient will receive practical instructions on how to self-administer the drug. The patient will be required to remain at the site for one hour after the first administration for observation. Any adverse events will be recorded in the CRF. The patient will self-administer subsequent 4 mg subcutaneous injections for the 84 day study drug period unless there is reason for discontinuation of the study drug.

Study medications should be injected subcutaneously in the front or side of the thigh daily, in the morning. Patients are advised to rotate daily injection sites to avoid injecting into the same area repeatedly. In the unlikely event that the patient is unable to inject into the thigh they may inject into the abdomen.

The patient will be provided with Study Drug Administration Guidelines to instruct them how to reconstitute the study drug for injection and how to administer the injection. The patient will also be provided with a Study Drug Diary Card and will be instructed to note each daily study drug administered.

The PI or designee should confirm that all study drugs are administered as per protocol by checking the returned Study Drug Diary Card. Any anomalies in study drug used/unused will be queried with the patient and in the event that the patient has not administered study drug, this will be recorded as a protocol deviation in the CRF.

The completed Study Drug Diary Card should be filed alongside the patient CRF.

9.6 Study Drug Termination

The study drug will be discontinued if any of the following conditions are met prior to the study drug treatment period of 12 weeks:

1. Patient or clinician request for withdrawal from the study.
2. Patients whose sight is determined as deteriorating to the point of a 10 letter drop in sight. The study drug will be stopped and the patient will be offered the current standard care treatment.

Whilst on the study enrolled participants, [i.e. patients with DMO and thick retinas (400 microns or more)] will be receiving the study drug rather than the current standard treatment (currently anti VEGF drugs in the NHS). Patients who wish to withdraw from the study, those in whom sight loss occurs during the duration of the study or those completing the study in who DMO persists, will be offered this standard care treatment.

10. PARTICIPANT TIMELINE: SCHEDULE OF ASSESSMENT AND DATA COLLECTION

10.1 Schedule of Assessments

All patients must be evaluated during the study according to the schedule of assessments outlined in Table 2.

Table 2: Schedule of Assessments

	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

10.2 Best Corrected Distance Visual Acuity

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.

10.3 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.

10.4 Retinal Perfusion, as Determined by Fundus Fluorescein Angiography

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.

10.5 Macular Function, as Determined by Macular Microperimetry

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.

10.6 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

10.7 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.

All outcomes will be recorded in CRFs or questionnaires specifically designed for the study.

10.8 Blood and Urine Sample

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)

10.9 Research Samples/Exploratory Analysis

The remaining part of the blood sample (10.8 above), will be used to test for ARA 290 antibodies and to complete an exploratory analysis to determine levels of inflammatory markers and carbamylated and glycosylated albumin.

The blood sample will be taken prior to ARA 290 administration at baseline, and at least 2 hours after the most recent treatment. Within 30 minutes after collection, the sample will be centrifuged at 3000 rpm for 10 minutes at 4˚C. The collected serum will be transferred to transport tubes [2 tubes for ARA 290 antibodies (approximately 0.5 mL per tube), 2 tubes for carbamylated albumin, 2 tubes for glycosylated albumin, and 2 tubes for immune markers (approximately 0.1 mL per tube)] and stored at -80˚C.

Patients leaving the study before study completion (i.e. week 12) will have a full evaluation like that being undertaken at the 12 week visit, unless the patient refuses consent for this evaluation to be undertaken.

10.9.1 ARA 290-Antibodies

After the last subject has the week 12 blood sample taken, one of the samples (0.5ml) of serum collected will be shipped on dry ice or liquid nitrogen via courier to The Charles River Laboratory in Montreal, Canada for analysis. The additional sample (0.5ml) of serum will be stored at the research center as back-up. The samples will be stored under code, which can be linked to subject's identity only by authorised personnel.

10.9.2 Inflammatory Biomarkers

A multiplex assay will be carried out to determine the presence of inflammatory biomarkers. Proseek Multiplex Inflammation assay is a proprietary (Olink Biosciences) methodology employing proximity extension assay technology to measure simultaneously 92 inflammation biomarkers. The volume of serum required for this purpose is 90 microliters. Details on this assay are available at www.olink.com

After the last subject has the week 12 sample taken, one of the samples (0.1ml) of serum collected will be shipped on dry ice or liquid nitrogen via courier to an appropriate laboratory for analysis. The additional sample (0.1 ml) of serum will be stored at the research center as back-up. The samples will be stored under code, which can be linked to subject's identity only by authorised personnel.

10.9.3 Carbamylated and Glycosylated Albumin

An assay will be carried out to determine levels of carbamylated albumin a measure of renal function and metabolic status and of glycosylated albumin, a marker of glucose control. After the last subject has the week 12 sample taken, one of the samples (0.1ml) of serum for each of the above (i.e. 0.1 ml of serum for the purpose of determining carbamylated albumin and 0.1 ml for serum for glycosylated albumin) collected will be shipped on dry ice or liquid nitrogen via courier to an appropriate laboratory for analysis. The additional sample (0.2 ml) of serum will be stored at the research center as back-up, in 2 x 0.1 ml aliquots. The samples will be stored under code, which can be linked to subject's identity only by authorised personnel.

On completion of the sample analysis and transfer of this to the CTU, all samples sent to the laboratories will be destroyed and confirmation of destruction will be sent to the CTU. On receipt of this confirmation, the CTU will confirm with the PI, at which point all back up samples will also be destroyed and confirmation of destruction will be sent to the CTU.

10.10 Telephone Checks

The PI or designee will contact the patient by telephone 2 weeks post enrolment onto the study to check compliance with study drug administration and to assess if the patient is experiencing any adverse events.

For those patients who withdraw from the trial/study drug prior to 12 weeks or following the completion of 12 weeks of treatment (and who do not need to attend the 16 week visit), the PI or designee will contact the patient by telephone 4 weeks post study drug termination to assess if the patient is experiencing any adverse events.

11. DATA COLLECTION & MANAGEMENT

11.1 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the protocol and using quality control measures to establish and maintain high standards for data quality.

The Chief Investigator (CI) and CTU will provide training to site staff on trial processes and procedures including the CRF and data collection.

On-site monitoring visits during the trial will check the accuracy of entries on CRF's against the source documents, the adherence to the protocol, procedures and Good Clinical Practice (GCP).

Quality control is implemented by the CTU in the form of Standard Operating Procedures (SOPs), which are defined to encompass aspects of the clinical data management process, and to ensure standardisation and adherence to International Conference of Harmonisation Good

Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

Data quality control checks will be carried out by the Data Manager to ensure 100% accuracy and data errors will be documented in Quality Control Reports with corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

A Data Monitoring & Ethics Committee (DMEC) will be convened for the study to carry out reviews of the study data at staged intervals during the study.

11.2 Data Collection

To ensure accurate, completed and reliable data are collected, the CTU will provide training to site staff in the format of investigator meetings and/or site initiation visits.

All data for an individual patient will be collected by the PI or designee and recorded in the CRF or questionnaires for the study. Patient identification on the CRF and questionnaires will be through their unique trial identifier, allocated at the time of recruitment, and patient initials. Data will be collected and recorded on the CRF by the PI or designee and the patient will complete the questionnaires from the time the patient is considered for entry into the trial through to their 12 week follow up, (or 16 week if at the 12 week follow up visit the patient's retina is dry).

CRFs and questionnaires are to be submitted to the CTU as per the CRF Submission Schedule, along with a CRF Tracking Form.

11.3 Data Management

Following the submission of CRFs and questionnaires to the CTU, the data will be processed as per the CTU Standard Operating Procedures (SOPs). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries and send them back to the CTU after they have been reviewed and signed by the PI or designee. Any amended information will then be entered in the study database. A copy of the signed data query form should be retained with the CRF at the investigator site.

12. STATISTICAL CONSIDERATIONS

12.1 Sample Size

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.

12.2 Data Analysis
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.

Given the short time course of the study (12 weeks), drop outs are not expected to occur.

12.3 Statistical Methods
Descriptive statistics will be used for the evaluation of primary and secondary outcomes. Differences in mean (SD) 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. 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 will be similarly evaluated. Exploratory analysis in relation to inflammatory markers and carbamylated and glycosylated albumin will also be observed from baseline to the week 12 visit. A Statistical Analysis Plan (SAP) will be created by the Trial Statistician, reviewed by the DMEC and approved by the CI.

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

13. PHARMACOVIGILANCE

Timely, accurate and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and is mandated by regulatory agencies.

The first ARA 290 Development Safety Update Report (DSUR) Report Number 01 (22 November 2013 – 30 November 2014) submitted by Araim Pharmaceuticals on 06th January 2015 reports that ARA 290 has been administered to 94 normal human volunteers and 166 subjects with sarcoidosis, diabetes, renal failure, rheumatoid arthritis, or critical limb ischemia, without any drug related Adverse Events (AEs) or laboratory abnormalities being reported. However, during the reporting period of the first DSUR there was one Serious Adverse Event (SAE) of suicidal thoughts in one patient on the APCP-112 study, European Clinical Trials Database (EudraCT) number 2013-003016-45. This patient was noted to have a history of depression. The patient was receiving a higher dose of ARA 290 (8 mg daily) than is proposed in this ARA 290-DMO study (4 mg daily). The relationship of study drug to the SAE was considered possible, although unexpected considering prior preclinical and clinical experience. In light of this SAE, Araim Pharmaceuticals sought advice from the Food and Drug Administration (FDA) who advised that a suicidal screening tool be used in subsequent studies. To comply with this, at baseline and at the 4, 8 and 12 week follow up visits all patients will also complete the Columbia Suicide Severity Rating Scale (C-SSRS) for potential suicidal ideation.

13.1 Definition of Adverse Events
The European Clinical Trials Directive 2001/20/EC and applicable clinical trial regulations set out the legal requirements for adverse event recording, management and reporting of clinical trials.

Table 3: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in: - The Summary of Product Characteristics (SmPC) for that product (for products with a marketing authorisation) or - The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)
Serious Adverse Event (SAE) Serious Adverse Reaction (SAR)	A SAE is an adverse event that: - results in death - is life-threatening - requires hospitalisation or prolongation of existing hospitalisation* - results in persistent or significant disability or incapacity - consists of a congenital anomaly or birth defect - is any other important medical event (s) that carries a real, not hypothetical, risk of one of the outcomes above. A SAR is an adverse reaction that is classed as serious and which is consistent with the information about the investigational medicinal product in question set out in the: - SmPC in the case of a licensed product. - IB for any other investigational product.
Suspected unexpected Serious Adverse Reaction (SUSAR)	A SUSAR is a serious adverse reaction which is unexpected i.e. the nature and severity of which is not consistent with the information about the medicinal product in question set out: - in the case of a product with a marketing authorisation, in the SmPC for that product - in the case of any other investigational medicinal product, in the IB relating to the trial in question.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute a SAE.

13.2 Eliciting Adverse Event Information

The PI or designee will record all directly observed AEs and all AEs spontaneously reported by the patient. In addition, the patient will be asked about AEs at each visit following initiation of treatment. The PI or designee must assess all AEs for seriousness, causality, severity and if the adverse event is related to the study drug for expectedness.

13.3 Assessment of Seriousness

The PI or designee should make an assessment of seriousness i.e. is this is an adverse event, adverse reaction or suspected unexpected adverse reaction that:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

13.4 Assessment of Causality

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the study drug:

- **Not Related:** Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Unlikely:** Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly*:** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- **Probably*:** Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
- **Definitely*:** Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

13.5 Assessment of Severity

The PI or designee should make an assessment of severity for each AE according to the following categories:

- **Mild (Grade 1):** A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate (Grade 2):** A reaction that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe (Grade 3):** A reaction that prevents normal everyday activities.
- **Life Threatening (Grade 4):** A reaction that has life threatening consequences; urgent intervention indicated.
- **Death (Grade 5):** A reaction that results in death.

13.6 Assessment of Expectedness

The PI or designee is required to make an assessment of expectedness based on any relevant product information as documented in the IB. Adverse reactions or serious adverse reactions may be classed as either

- **Expected:** The AR is consistent with the toxicity of the study drug listed in the IB.
- **Unexpected:** The AR is not consistent with the toxicity in the IB.

An AR may be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.

13.7 Adverse Event Reporting Period

The AE reporting period for the trial begins upon enrolment into the trial and ends 30 days following the last administration of the study drug. All AEs assessed by the PI as possibly, probably or definitely related to the study drug and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

13.8 Adverse Event Reporting

All AEs should be reported on the AE form within the CRF. An adverse reaction (AR) is an AE which is related to the administration of the study drug. All ARs must be reported on the AE form within the CRF.
An unexpected adverse reaction (UAR) is an AE which is related to the administration of the study drug and that is unexpected, in that it has not been previously reported in the current IB. All UARs must be reported on the AE form within the CRF.

These events will be included as part of the safety analysis for the trial and do not require expedited reporting to the CTU.

13.9 Serious Adverse Event Reporting

A SAE is defined as an AE that fulfils one or more of the criteria for seriousness outlined in Table 3. SAEs that are related to the administration of the study drug are SARs. SUSARs are SAEs that are considered to be caused by the study drug and are unexpected i.e. their nature or severity is not consistent with the IB. All SAEs, SARs and SUSARs must be reported to the CTU.

If a SAE occurs, reporting will follow the regulatory requirements as appropriate and all SUSARs will be the subject of expedited reporting. SAEs will be evaluated by the PI for causality (i.e. their relationship to study drug) and expectedness (if related). SAEs will be reported using the SAE Form and must be reported to the CTU within 24 hours of becoming aware of the event. The PI should not wait until all information about the event is available before notifying the CTU of the SAE. The CTU will acknowledge receipt of the SAE Form within two working days by email to the site. Information not available at the time of the initial report must be documented on a follow up SAE Form. Follow up information should be sought and submitted as it becomes available. The follow up information should describe whether the event has resolved or persists, if and how it was treated and whether the patient continues on the study or has been withdrawn from treatment.

The CTU is responsible for reporting SAEs to the Sponsor, ethics committee, and MHRA within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the CTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and research ethics committees within 15 days after the knowledge of such an event.

13.10 Recording and Reporting of Urgent Safety Measures

In the event that the CI becomes aware of information that necessitates an immediate change in study procedure, to protect clinical trial subjects from any immediate hazard to their health and safety the CI should phone the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately once an urgent safety measure has been taken at site.

Following this initial telephone call the CI must immediately report to the Sponsor who will inform MHRA and REC in writing within 3 days of the incident. Written notification in the form of a substantial amendment is also required.

The CTU will assist the CI to ensure adherence to reporting requirements to REC and MHRA and must be kept fully informed of any changes implemented or required.

13.11 Pregnancy

13.11.1 Contraceptive Advice

While ARA 290 has not been shown to adversely affect pregnancy or harm the fetus in two animal studies, it is an investigational drug and therefore pregnant or breast feeding women will be excluded from the study. A pregnancy test will be performed in every woman of child-bearing age before she is included into the study. All non-pregnant women of child-bearing age will be instructed at the beginning of the study, before receiving the study drug, that it is essential that they use effective contraception to prevent pregnancy e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom. This contraceptive should be continued for at least 30 days post administration of the final dose of the study drug. Women who refuse to take effective contraception will not be permitted to enter the study, and women who stop using effective contraception during the course of the study will be discontinued from study participation.

Male study participants will be advised that they should not father a child during this study and for a safety period of 30 days after final treatment. To ensure this, male participants will be advised that they or their partner must use reliable forms of contraceptive during the trial and for 30 days afterwards, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom.

13.11.2 Pregnancy Reporting

Women who become pregnant during the study should stop ARA 290 immediately and inform the PI. Male study participants should inform the PI if their partner becomes pregnant while he is in the study. Pregnancy is not considered an AE or SAE, however an abnormal outcome would be. Therefore the PI or designee must collect pregnancy information for female participants, and for females who become pregnant while their partners are participating in the trial. Consent should be obtained to follow up the pregnancy from the female partners of male participants.

The pregnancy reporting period for the trial is from the commencement of the study drug until 30 days post admin of the final dose of study drug. The PI or designee should complete and submit the Pregnancy Reporting Form to the CTU by email within 14 days of being made aware of the pregnancy. The CTU will acknowledge receipt of the Pregnancy Reporting Form within two working days by email to the site.

Any pregnancy that occurs in a participant or participant's partner during the trial should be followed to outcome. Follow up/outcome information should be provided to the CTU as soon as it becomes available. Araim Pharmaceuticals, Inc. may also request their consent to collect confidential information about their health and that of the baby.

An unwillingness to undertake adequate precautions to prevent pregnancy for the duration of the trial is an exclusion criteria for this study.

14 DATA MONITORING

14.1 Data Access

Prior to commencement of the study, the PI will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients for direct access to data will also be obtained. The patients' confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.2 Monitoring Arrangements

The CTU will be responsible for trial monitoring. On-site monitoring visits will be conducted in accordance with the trial monitoring plan. On-site monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of Good Clinical Practice (GCP) and European Union (EU) directive 2001/20/EC. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating site, an initiation visit will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. On-site monitoring visits during the trial will check the accuracy of entries on CRF's against the source documents, the adherence to the protocol, procedures and GCP, and the progress of patient recruitment and follow up. Monitoring will also ensure that the trial drug is being stored, dispensed and accounted for according to specifications.

The PI or designee should ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

The site close out procedure will commence following the completion of the 12 week follow up period of the final patient (16 weeks in the event that the patient retina is dry at the 12 week visit).

15. TRIAL COMMITTEES

15.1 Trial Management Arrangements

The CI will have overall responsibility for the conduct of the study. As this study is a single site study, the CI will also act as PI. The CTU will undertake trial management including all clinical trial applications (MHRA, ethics, and research governance), IMP management, pharmacovigilance, site initiation/training, monitoring, analysis and reporting. The Trial Manager will be responsible on a day to day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team, and will be the main contact between the trial team (section 2) and other parties involved. The CTU will assist and facilitate in the setting up and co-ordination of the trial committees including the Trial Management Group (TMG) and Data Monitoring and Ethics Committee (DMEC).

15.2 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.

15.3 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 & Muscoskeletal 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 Steele, Honorary Clinical Senior Lecturer, Institute of Genetic Medicine, Newcastle University

Dr Sobha Sivaprasad, Consultant Ophthalmologist, Moorfield Eye Hospital, 162 City Road, London, EC1V 2PD

16. REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Research Governance Framework.

16.1 Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor delegated duties in relation to the management of the study.

16.2 Funding

This study is funded by ARAIM PHARMACEUTICALS, INC. 580 White Plains Road, Suite 210, Tarrytown, NY 10591 USA. Funding provided by Araim Pharmaceuticals covers the costs for staff based at the Clinical Trials Unit (CTU) the trial co-ordinating centre for the study, staff costs incurred by participating sites (including Research Nurse, Photographer and Optometrists time), study consumables and pharmacy costs. Araim Pharmaceuticals Inc. will also supply the investigational medicinal product (IMP) for the study.

16.3 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to patients by the design of the research protocol through the Clinical Negligence Fund in Northern Ireland.

16.4 Contributorship

The CI conceived and designed the study protocol with input from Araim Pharmaceuticals. The CI is also the grant holder and will oversee the management and conduct of the study.

The Trial Statistician and Trial Manager from the NICTU contributed to the development of the protocol and study design. The Trial Statistician provided statistical advice and will oversee the analysis. The BHSCT Pharmacist contributed to the development of the protocol and provided pharmaceutical advice.

16.5 Competing Interests

The research costs including the cost of the intervention were funded by Araim Pharmaceuticals. The CI and members of the TMG have no financial or non-financial competing interests and the members of the DMEC will be asked to confirm that they have no conflict of interest. In the event that a DMEC member reports a conflict of interest, advice will be sought from the Sponsor.

16.6 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

A Clinical Trial Authorisation (CTA) will be obtained from the Medicines for Human Use Regulatory Authority (MHRA) before the start of the trial.

16.7 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

16.8 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the Sponsor within one working day of becoming aware of the breach.

16.9 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the Regulatory Authority. Changes to the protocol may require regulatory authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to patients. The CTU in collaboration with the sponsor will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations. Protocol compliance will be monitored by the CTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRF's, patient consent) is being completed appropriately.

16.10 Patient Confidentiality

In order to maintain confidentiality, all study reports and communication regarding the study will identify the patients by the assigned unique trial identifier only.
Computers where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

16.11 Post-trial Care

Once the trial is completed, patients who participated in the study and who still present with DMO will revert to the NHS standard of care. If no DMO is present, observation will be recommended.

16.12 Record Retention

The PI will be provided with an ISF by the CTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The Trial Master File (TMF) will be held by the CTU within the BHSCT and the essential documents that make up the file will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the CTU according to the applicable regulatory requirements and for up to 15 years as required by the BHSCT Sponsor. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the CTU and Sponsor.

17. DISSEMINATION/PUBLICATIONS

17.1 Trial Publications

The final study report will be provided by the Trial Statistician; it is anticipated that the study findings will be published in national and international peer review journals which will be led by the CI. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health care professionals. In addition study findings may be presented at both national and international meetings and also to appropriate patient groups.

Upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. The most significant results will be communicated to the public through press releases. An on-going update of the trial will also be provided on the NICTU website.

17.2 Authorship Policy

An author will be considered to be someone who has made a substantive intellectual contribution to the study. All investigators, Trial Statistician and relevant members of the Trial Management Group will potentially be co-authors. Contributors from Araim Pharmaceuticals Inc. will also be co-authors. Collaborators will be acknowledged.

17.3 Trial Registration

The trial will be registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database and the International Standard Randomised Controlled Trial Number (ISRCTN) register.

17.4 Data Sharing Statement

The trial data will be shared with Araim Pharmaceuticals Inc.

17.5 Data Access

Following the publication of the primary and secondary study outcomes, there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI who will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of “[name] on behalf of the ARA 290-DMO Clinical Trial Group” or something similar which will be agreed by the TMG.

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