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Oral glycoside supplement (triterpenoid saponins) for early and intermediate stage age-related macular degeneration (SAMADI trial): study protocol for a double masked randomised placebo-controlled feasibility trial.

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Abstract

Background: The primary aim of the SAMADI [SAponins for MAcular DIsease] trial is to establish whether treatment of age-related macular degeneration (AMD) with oral saponin supplements is feasible and acceptable to participants. AMD is a progressive disease, which results in the death and dysfunction of cells in the outer retina. One potential contributor to AMD progression is the reduced permeability of Bruch's membrane underlying the retina. Saponins have a structure enabling them to assist dispersal of lipid deposits in Bruch's membrane, providing a rationale for the proposed intervention in AMD. Secondary aims are to provide an estimate of the variability of a proposed future primary outcome, and to provide estimates of treatment effects of clinical outcomes.

Methods: SAMADI is a double masked randomised feasibility trial, which will recruit 60 participants with early or intermediate AMD in at least one eye. Participants will be randomly assigned into one of two groups, one receiving the oral saponin tablets and the other placebo tablets (indistinguishable in appearance), both to be taken daily for 4 months. Participants and research optometrists will be masked to the allocation. Clinical tests will be repeated at baseline, 4 months and 12 months. The primary outcome measures relate to feasibility of the following aspects of the intervention and study design: 1) recruitment and retention over 4 and 12 months; 2) adherence to treatment and acceptability of intervention; 3) the eligibility assessment process; 4) collecting the outcome data. The rate of serious adverse events will be an additional primary outcome measure.

Secondary outcomes include dark adaptation metrics, best corrected visual acuity, contrast sensitivity, fundus imaging, low luminance questionnaire, standard electroretinograms according to International Society for Clinical Electrophysiology of Vision standard protocols, and imaging retinal densitometry (at one site only).

Discussion: The data will be used to determine the feasibility of the trial design, how well participants complied with taking the tablets, and the potential effectiveness of the treatment. If feasible, this information will be used to inform a larger trial, which will definitively assess how effective the treatment is in participants with AMD.

Trial registration:

The trial is registered with EudraCT and ISRCTN registries.

EudraCT ref: 2021-003045-38; Date of registration: 24/05/2021

ISRCTN ref: ISRCTN82949875; Date of registration: 21/07/2021

URL: https://www.isrctn.com/ISRCTN82949875

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Keywords

Randomised controlled trial; age-related macular degeneration; saponins; feasibility study;

Introduction

Background and rationale

Age-related macular degeneration (AMD) is a progressive condition, which ultimately results in the dysfunction and death of the light sensitive cells in the retina: the photoreceptors. Globally, AMD is the second most prevalent cause of unavoidable blindness (1).

Photoreceptor cells are metabolically supported by delivery of nutrients from the blood supply underlying the retina, across Bruch's membrane and the retinal pigment epithelium (RPE), and by the removal of toxic waste products in the opposite direction. With age, there is accumulation of deposits rich in lipids and denatured proteins in Bruch's membrane, resulting in an exponential decrease in transport capability. In AMD, these changes in Bruch's membrane are accelerated, compromising metabolic support to photoreceptors leading to their death, and thus vision loss. An obvious intervention in the disease would be to remove the deposits and rejuvenate the metabolic support to photoreceptor cells.

Saponins are principally extracted from two sources, the ginseng plant and sea cucumber marine animals (2), and have been used as food or nutritional supplements for thousands of years without any side effects (3). The saponin molecules are a group of tri-terpenoid aglycones linked to one or more oligosaccharides by glycosidic linkage, often referred to as glycosides. They are amphipathic molecules that have hydrophilic and hydrophobic domains due to the presence of carbohydrate and triterpenoid regions respectively. Therefore, they can readily partition into lipid structures such as liposomes, micelles, membranes, and lipoidal deposits to assist dispersal (4–7). Since the major deposits in Bruch's membrane are lipids, this ability of saponins to disperse lipid-rich deposits provides a rationale for the proposed intervention in AMD.

Saponins are claimed to be beneficial for maintaining normal health and have been used to address many diseases. Their increased use as nutritional supplements in industrialised countries has prompted scientific investigations regarding the claims. Major areas of investigation have been the cardiovascular system (8–10), glucose metabolism in relation to type 2 diabetes (11,12), anti-cancer properties, psychomotor function regarding stress and Alzheimer's disease (13,14), potential for

intervention in pulmonary diseases (15,16), and effects on sexual erectile dysfunction (17). There were no adverse effects in any of the many clinical trials with saponins. Rare cases of mild insomnia, diarrhoea, nausea and vomiting, headache and gastric discomfort (dyspepsia) have been reported but were only transitory (2,3). Some controversy remains as to whether saponins interfere with warfarin anti-coagulant therapy. Detailed animal studies suggest that interference with warfarin can occur but only at moderate to high saponin doses (18). Breathing problems, tightness in the throat, chest pain, skin hives, rash or itchy or swollen skin may mean a participant is allergic to sea cucumber products (3). As such, a known or suspected seafood allergy is listed as a trial exclusion criterion.

There is no animal model of AMD that mimics the grossly altered structural and functional aspects of human Bruch's membrane. However, the proof of principle for saponin use in AMD has been demonstrated using donor human Bruch's membrane. Results showed that saponins could indeed remove the deposits and improve the transportation characteristics of Bruch's membrane (19). AltRegen Co Ltd. have also undertaken pilot clinical studies to assess usefulness of saponins in AMD. In AMD, recovery of light sensitivity after a bright flash is impaired due to reduced transport of 11-cis retinal to photoreceptors. Saponin supplementation in the six participants with AMD tested showed marked improvement in recovery of light sensitivity compared to those receiving a placebo control (20).

Rationale for current trial

Whilst oral glycoside (triterpenoid saponins) supplementation is a promising new therapy for early and intermediate stage AMD, currently there is insufficient evidence to licence the compound as a therapy for AMD or to support its use in this participant group. The decision whether to use a single saponin or a mixture for therapeutic intervention is dependent on the nature of the proposed target. In Bruch's membrane, the target comprises a multitude of lipid classes with each class having many members (21). In addition, there is a wide spectrum of denatured and aggregated proteinaceous species (21). A single saponin species is highly unlikely to have similar affinities towards all the deposited species. Saponins derived from ginseng and sea cucumbers have different affinities for the varied lipid classes (unpublished data) and therefore a mixture would be best suited to target these

deposits in Bruch's membrane. Thus, the proposed investigational product is a mixture of ginseng and sea cucumber extracts containing the various saponins.

Given that oral glucoside (triterpenoid saponins) supplementation is an established 'food supplement' that has been used for centuries we do not expect significant safety issues (see Manan et al, 2016 for a review of the safety of sea cucumber containing products) i.e. there is no need for a Phase I trial (3). Previous pre-clinical work has identified the therapeutic dose and this has been tested in a small number of people with AMD (20). However, currently there is insufficient data to determine how many people would be needed in a definitive Phase III trial. Hence, we propose to undertake a Phase IIb clinical trial. Estimates of the variation in the proposed primary outcome measure are essential for the planning of the Phase III trial. The level of saponins in the therapeutic formulation intended for use in this trial is within those of commercially available supplements.

Given the underlying hypothesis that oral glycoside supplementation will have a beneficial effect on transport across Bruch's membrane, our key clinical outcome measures will be metrics associated with dark adaptation. This is because dark adaptation, the rate at which people regain visual sensitivity in the dark after light exposure, is dependent on the regeneration of light sensitive visual pigment located in the outer layer of the retina. The speed with which this process occurs is dependent on the rate of transport of metabolites across Bruch's membrane i.e. the parameter we are measuring in the trial is closely related to the tissue being targeted by the intervention (22,23). In addition, to ensure the results of this trial can be compared to others, we propose to include a battery of well validated clinical outcome measures, including the participant reported low luminance questionnaire (24). Furthermore, to demonstrate safety, we shall also include the standard ISCEV electrophysiological protocol (25).

Objectives

The aim of the SAMADI trial is to determine the feasibility of a randomised controlled trial of a 117mg dose of 'triterpenoid saponins' (the active ingredient in glucoside supplementation) vs. a placebo in people with early and intermediate stage AMD.

The primary objective is to establish the feasibility (including recruitment, retention, adherence, acceptability) of triterpenoid saponins in participants with early and

intermediate stage AMD. Secondary objectives are (i) to provide an estimate of the variability of a proposed future primary outcome for the estimation of the sample size for a Phase III RCT and (ii) to provide estimates of treatment effects of clinical outcomes in order to identify the most sensitive dark adaptation metric, identify redundant outcome measures and optimise the acceptability of the trial to future participants.

The aim of a clinical sub-study which will be carried out at the Cardiff site only is to collect preliminary clinical data on the performance of the imaging retinal densitometer (IRD, a non CE-marked device) in an approved RCT where characteristics of participants are well defined. Specifically, we aim to determine rod and cone visual pigment synthesis rates collected using IRD at baseline, 4 and 12 months from the Cardiff site only and compare these metrics to those obtained with the more conventional outcomes. We will also evaluate the effect of the treatment (placebo vs IMP) on IRD metrics.

Trial design

This trial is an exploratory (Phase IIb), two arm, double-masked, randomised, placebo-controlled feasibility clinical trial of ginseng and sea cucumber extract ('triterpenoid saponins', 117mg daily for 4 months for early and intermediate stage AMD).

Recruited participants will be randomly allocated to active treatment or placebo (1:1) using online randomisation to preserve allocation concealment from the recruiter and balanced using blocked randomisation to maintain balance of numbers between arms, stratified by site and AMD severity. Follow-up data collection will be at 4 and 12 months using electronic case report forms (eCRFs) and optometry assessments. The end of the trial will be defined as the date of final data capture to meet the trial endpoints.

The clinical evaluation of the non-CE marked IRD device, incorporated as a sub-study at the Cardiff site will be a single centre feasibility study. Visual pigment kinetics will be measured in all participants at the Cardiff site as part of their main trial assessments regardless of whether they are allocated to IMP or placebo in the main trial.

Methods: Participants, interventions and outcomes

Study setting

The trial will be carried out in two participating sites within the UK (Cardiff University Eye Clinic and School of Optometry and Vision Sciences; Department of Optometry and Visual Sciences, City St George's, University of London). Both sites are university-based and provide eye care services to the general public and participants referred via the NHS. A total of 60 participants will be recruited at an expected rate of 3-4 per month per site.

Eligibility criteria

To be eligible for inclusion, participants will be aged 60 to 85 years old (inclusive), able to provide informed consent and comply with the trial visit schedule, and have AMD in both eyes, which will be of early or intermediate stage in at least one eye (26). If both eyes have early or intermediate stage AMD, the eye with the better acuity will be selected as the trial eye. If both eyes have the same acuity, we will use the trial eye randomisation list to select the trial eye.

Individuals will be excluded from participating in the trial if they have non-AMD ocular pathology in the study eye (or in either eye for genetic conditions or glaucoma), a diagnosis of systemic disease including diabetes, vitamin A deficiency, cancer undergoing active treatment, cancer with ocular involvement, or any other significant systemic disease or medication known to affect visual function or which would compromise participation in a one year trial. Additional exclusion criteria are an intraocular pressure of 24 mmHg or greater, grade <2 van Herick (27) or history of allergic reaction to dilating eye drops, lens opacity greater than grade 2 on any Lens Opacity Classification System (LOCS III) criterion (28), or other media opacity/ nystagmus that might interfere with quality retinal imaging, inability to classify AMD grade, insufficient English language comprehension to understand the Low Luminance Questionnaire, a possible cognitive impairment as determined using an abridged Mini-Cog (score <3) (29), known or suspected seafood allergy, photosensitive epilepsy, current treatment with Warfarin or other vitamin K antagonists (Phenindione, Acenocoumarol), participation in any other interventional trial within 30 days prior to entering this trial, men who are planning a pregnancy with their partner or have partners who are women of childbearing potential, taking

supplements containing saponins (e.g. ginseng), unable to consume the IMP or placebo for a period of longer than 24 hours during the treatment window, or patients undergoing planned, forthcoming major surgical interventions.

The eligibility of each potential participant will be confirmed by an Ophthalmologist following review of GP provided medical history and initial screening by the research optometrist.

Who will take informed consent?

Informed consent will be obtained by any authorised member of the trial team delegated to do so. This will include research optometrists with certified training in the tenets of Good Clinical Practice (GCP).

Additional consent provisions for collection and use of participant data and biological specimens

The researcher will discuss each section of the participant information sheet with the potential participant to ensure understanding, provide an opportunity to ask questions and remind them that they may withdraw consent at any time without reason. Once satisfied that the potential participant understands the trial, written informed consent will be obtained using the trial Consent Form. The participant information sheet explicitly discusses the provisions for the collection and use of participant data, as well as the provisions made to ensure that the data is treated in a GDPR compliant manner. Translations of patient information sheets & consents will be available for any participants where Welsh is their first language.

Interventions

Explanation for the choice of comparators

There is no validated treatment for early or intermediate stage AMD, hence the choice of a placebo control comparator. The placebo control will consist of four tablets per day, taken following the same schedule as the intervention. The placebo tablets are visually identical to the IMP and contain inactive excipients.

Intervention description

The intervention is supplied as tablets containing a proprietary mixture of ginseng and sea cucumber extracts as the source of triterpenoid saponins, together with antioxidant vitamins and taurine. The active treatment provides a total daily dose of 117 mg of triterpenoid saponins, administered as four tablets daily for 4 months.

Two tablets will be taken in the morning and two in the evening, swallowed whole with water after food.

Criteria for discontinuing or modifying allocated interventions

Breathing problems, tightness in the throat, chest pain, skin hives, rash or itchy or swollen skin may mean a participant is allergic to sea cucumber products. For this reason, known or suspected seafood allergy is an exclusion criterion. However, if such a hypersensitivity reaction were to occur, the participant will stop taking the trial treatment immediately. If participants present at A&E (e.g. for an allergic reaction) then the participant's contact card will instruct the treating emergency physician to treat the participant as if they were in the active arm and receiving the intervention and tailor their care accordingly, involving cessation of the intervention.

In the case of a serious adverse event arising in the course of the trial, which is considered by the trial physician to be potentially related to the intervention, participants will be advised to cease the intervention. Additionally, if the participant develops advanced AMD in the study eye, they will be asked to cease the intervention.

Strategies to improve adherence to interventions

Each participant will be given a diary to fill in, detailing their adherence to the treatment regime each day. They will also receive a monthly telephone call from the research optometrist at the end of months 1-3, in which a structured treatment questionnaire will be administered, asking participants about any issues taking the tablets, any lapses in adherence, and how many tablets remain in the current bottle. At the end of the trial, the participant will return their completed adherence diary and any remaining tablets to the research optometrist.

Relevant concomitant care permitted or prohibited during the trial

As a precaution, participants currently taking warfarin and other vitamin K antagonists (Phenindione, Acenocoumarol) will be excluded from the trial. In addition, participants will not be able to take supplements containing ginseng during their period of participation in the trial.

Other currently prescribed medications are permitted unless specifically contraindicated as detailed above. Concomitant medications will be recorded at baseline and the 4 month and 12 month follow-up. Participants will be advised not to start taking any new supplements during the trial. If they are already taking a supplement(s) at baseline, this will be recorded at baseline, and also at the 4 month and 12 month follow-up timepoints.

Provisions for post-trial care

The 12 month follow-up appointment will take place 8 months after cessation of the treatment. At this timepoint the eyes will be examined and questionnaires regarding treatment acceptability and adverse events carried out. Any adverse events that occur within the 12 month timeframe will be recorded, reviewed by a medical doctor affiliated with the trial, and reported according to MHRA guidelines. During this time, the participants will be able to contact the trial team 7 days per week with any urgent concerns. Further adverse events associated with the intervention are highly unlikely to arise after this timeframe, but participants will still be able to contact the trial team on the site email or telephone number if concerns arise.

Outcomes

The primary outcome measures relate to feasibility of the following aspects of the intervention and study design: 1) recruitment into the trial; 2) retention over 4 and 12 months; 3) adherence to treatment; 4) acceptability of intervention; 5) the eligibility assessment process; 6) collecting the outcome data. Additionally, the rate of serious adverse events including comparative rates between arms will be an additional primary outcome measure.

Secondary outcome measures include dark adaptation metrics at 4 and 12 months

including time constant of cone recovery (cone tau), rod-cone break time, final cone threshold as measured psychophysically using an established technique (30–32) and the slope of the S2 component of the rod dark adaptation function (envisaged to be the primary outcome measure in any future Phase III trial).

To further benchmark retinal status (i.e. facilitate cross-trial comparisons) and demonstrate safety, a number of secondary outcome measures are collected at each timepoint (4 months and 12 months) i.e. best corrected visual acuity (BCVA; Early Treatment of Diabetic Retinopathy Study [ETDRS] chart), contrast sensitivity (Pelli-Robson), AMD status according to Beckman grade, assessed using colour fundus photography (26), total retinal thickness and RPE-Bruch's complex thickness averaged in 9 sub fields of the ETDRS grid, measuring using spectral domain optical coherence tomography (SD-OCT; Spectralis, Heidleberg), score on a validated patient reported outcome measure assessing vision in low luminance conditions (the Low Luminance Questionnaire [LLQ]), amplitudes and times to peak of electroretinogram (ERG) subcomponents recorded according to standard International Society for Clinical Electrophysiology of Vision (ISCEV) recording guidelines (25), and the rod and cone optical density and visual pigment synthesis rates and optical density determined using imaging retinal densitometry (Cardiff site only) (33).

Participant timeline

The timeline of participant activity is shown in Table 1. All outcomes measured at baseline will be assessed at 4 months and 12-months after the date of randomisation. There will be two visits per timepoint.

Baseline visit 2 will occur ideally within 2 weeks but can take place up to 4 weeks after baseline visit 1. The 4-month follow-up and 12-month follow-up timepoints will be calculated from the date of randomisation and can occur up to 4 weeks after the required date. Participants will be sent reminders via a chosen method(s) of contact for each trial visit 2-4 days prior to the appointment. The participant will also be contacted by telephone at month 1, 2 and 3 (-1/+2 weeks) to assess treatment compliance, monitor adverse events, and remind them to take their medication.

Procedures (in Chronological order)	**Baseline Visit 1**	**Baseline Visit 2***	**Compliance**	**Compliance telephone**	**Compliance telephone**	**Follow up 1 Visit 1**	**Follow up 1 Visit 2***	**Follow up 2 Visit 1**	**Follow up 2 Visit 2***	**CI/PI telephones**
Time (months)	**0**	**0**	**1**	**2**	**3**	**4**	**4**	**12**	**12**	
1. Informed consent$	X									
2. Demographics$	X									
3. Medical & ocular history$	X									
4. Concomitant medications$	X					X		X		
5. Mini Cog$	X									
6. Refraction	X					X		X		
7. Visual acuity$	X					X		X		
8. Contrast sensitivity	X					X		X		
9. Irido-corneal angle assessment$	X									
10. Lens clarity assessment$	X									
11. Assessment of intraocular pressures	X									
12. Pupillary Dilation$	X	X				X	X	X	X	
13. Low luminance questionnaire		X					X		X	
14. NIR cSLO imaging$	X					X		X		
15. SD-OCT imaging$	X					X		X		
16. Eligibility assessment$	X									
17. 30 minutes rest	X					X		X		
18. Imaging retinal densitometry**		X					X		X	
19. Electroretinography		X					X		X	
20. Dark adaptometry	X					X		X		
21. Colour retinal photography$	X					X		X		
22. End of Treatment Questionnaire						X				

23. Randomisation		X								
24. Dispensing of trial drugs		X								
25. Adherence / Compliance		X	X	X	X	X				
26. Adverse event assessments			X	X	X	X	X	X	X	
27. Participant end of trial questionnaire										X

Table 1. Sprit Diagram showing timeline of participant activity, including schedule of enrolment, interventions and assessments[1].
*Second visit can be up to 4 weeks after the first visit
** At Cardiff site only (approximately 30 participants)
*** Participants will be asked at Follow up 2 Visit 2 if they are willing to be contacted by the PI or Research Associates by telephone to answer the end of trial questionnaire.
$ denotes the assessments that form part of the eligibility assessments.

Sample size

This exploratory trial has not been powered to evaluate effectiveness of the treatment. The sample of 60 participants will allow us to estimate predicted recruitment and retention rate in a future randomised feasibility trial. The estimates of variability of the outcome measures, and of the potential magnitude of any effect will allow us the plan a subsequent fully powered trial. Using a simple confidence interval for a single proportion, when the sample size is 60, a two-sided 95% confidence interval for a single proportion will range from 0.799 to 0.953 when the sample proportion is 0.9. The confidence interval was calculated using the Wilson Score Method (34).

Recruitment

Potentially eligible participants will be identified through a database of previous research participants at the two research centres, through volunteers registered with the Macular Society (a UK based charity for people with macular conditions), and from patients attending clinic appointments at local NHS institutions, such as hospital medical retina clinics, Optometrist practices, and GP practices, and at Cardiff University Eye Clinic and City St George's City Sight Eye Clinic. Potentially eligible participants will be provided with a participant information sheet (PIS). The PIS, and any advertisements, will invite interested participants to contact the participating sites. The researcher will then discuss the trial with the participant, either over the

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telephone or at their routine clinic visit, and then invite them to attend a screening visit (referred to as baseline visit 1) at the participating site.

Assignment of interventions: allocation

Sequence generation

Randomisation will be by blocked randomisation stratified by site and AMD severity. For stratification purposes, AMD severity will be classified as low or high risk (0-2 risk factors, or 2-4 risk factors on the Age Related Eye Disease Study [AREDS] simplified severity scale, respectively) (35). Each trial treatment pack (active or placebo) will be labelled with a unique identification number (pack ID). The online study database will allocate a pack ID for each participant.

Concealment mechanism

Eligible participants will be remotely randomised using an online computerised randomisation system created by the Centre for Clinical Trials Research (CTR) at Cardiff University, which will be operational 24 hours a day. If the online randomisation system is unavailable, the delegated randomiser will contact the CTR by telephone and a separate back-up manual randomisation list will be used to allocate the treatment and pack ID. Any participants randomised from the manual back-up list will be reconciled with the main computer-based list once the computer system is back up and running.

The research team will have no access to the underlying randomisation sequence at any time and will only be provided with the pack ID of the assigned treatment pack. The unique participant's trial IDs and pack IDs will be linked in the randomisation file, which will only be accessible by a statistician who is independent of the trial.

Implementation

Participants will be randomised to either active treatment or placebo. The allocation sequence will be created by an independent statistician at the CTR, who is not part of the trial research team. Enrolment and randomisation will be carried out by site Research Associates and Principal Investigators, to whom the role has been officially delegated. Randomisation will only be performed after the participant has signed the consent form and completed the screening and baseline assessments. Both the participant's trial ID and pack ID will be entered onto the CRF by the randomiser.

The CTR will also be notified that a participant has been randomised via an automated e-mail alert mechanism.

Assignment of interventions: Blinding

As SAMADI is a double-masked trial, the participants, treating optometrists and clinicians, and the trial team (including the trial statistician and researchers/ optometrists conducting all assessments) will be unaware of the group to which the participant has been allocated for the duration of the trial.

If participants present at accident and emergency (e.g. for an allergic reaction) then the contact card will instruct the treating emergency physician to treat the participant as if they were in the active arm and receiving the IMP and tailor their care accordingly, involving cessation of the IMP. The Chief Investigator (CI) and site Principal Investigator (PI) will be informed immediately. Unblinding is only performed in emergency situations where knowledge of the identity of the trial treatment is considered absolutely necessary for the clinical management of the participant, or if there is another compelling medical or safety reason to do so.

The CTR Safety team at Cardiff University will perform unblinding. Any out of hours unblinding, including the weekend and bank holidays, will be performed by the Site PI. Relevant contact information will be on a participant contact card, which the participant will be asked to carry with them, always. At the end of the trial, all participants will be made aware of their allocation at the same time as being provided with a summary of the trial results.

Data collection and management

Plans for assessment and collection of outcomes

Data will be recorded on electronic case report forms (eCRF), designed and maintained by the CTR at Cardiff University. The source data used to inform the eCRF for each of the outcomes/procedures is outlined in Table 2.

	Source Data						
Procedures (in Chronological order)	*eCRF (Case report form)*	*Recorded data (eg. Medical Device)*	*Participant Diary*	*Medical notes*	*PIS & Consent form*	*Questionnaire*	*SAE form*
1. Informed consent					x		
2. Demographics	x						
3. Medical & ocular history (patient reported)	x						
3b. Medical & ocular history (GP medical history)				x			
4. Concomitant medications	x						
5. Mini Cog						x	
6. Refraction	x						
7. Visual acuity	x						
8. Contrast sensitivity	x						
9. Irido-corneal angle assessment	x						
10. Lens clarity assessment	x						
11. Assessment of Intraocular pressures	x						
12. Pupillary Dilation	x						
13. Low luminance questionnaire	x						
14. Colour retinal photography		X					
15. NIR cSLO imaging		X					
16. SD-OCT imaging		X					
17. Eligibility assessment	x						
18. 30 minutes rest							
19. Imaging retinal densitometry**		X					
20. Electroretinography		X					
21. Dark adaptometry		X					
22. End of treatment questionnaire	x						
23. Randomisation	x						

24. Dispensing of trial drugs	x						
25. Adherence / Compliance			x				
26. Adverse event assessments	x						x
27. SAE assessments							x
28. Participant feedback questionnaire	x					x	

Table 2: Source data for the trial

The primary outcomes relating to feasibility of the trial and intervention will be assessed in various ways. Recruitment into the trial and data regarding the eligibility assessment process will be monitored using the screening log. This will include data, not only on numbers enrolled into the trial, but also regarding all ineligible and eligible but not consented/not approached participants. Data regarding adherence to treatment and acceptability of the intervention will be collected by means of a daily compliance diary, a monthly telephone questionnaire, and collection of remaining tablets at the end of the trial. Adverse events will be monitored using adverse events reporting forms, with a questionnaire regarding adverse events carried out in each monthly telephone call (months 1-3), and at the four and twelve month follow ups.

Dark adaptation metrics (a secondary outcome measure) will be obtained from the modelling of psychophysically assessed data using an established technique (30–32). The equipment used consists of a calibrated, high resolution computer monitor (Iiyama LS 902UT) and driven by an 8-bit (nVIDIA Geforce 9) graphics board under software control (Matlab, Math- works, Cambridge, UK). Dark adaptation will be monitored using the psychophysical methods previously described and implemented by Jackson et al (32). The procedure involves the participant being exposed to a bright adapting light provided by a hand-held light source consisting of an array of ‘white’ LEDs overlaid with a diffusing (LEE Filters 216 ‘white diffusion’) and amber filter (LEE Filters HT015 ‘deep straw’) to deliver a 60 second light of retinal illuminance 5.20 log phot Td.s^{-1} (bleaching approximately 85% of cone and 74% of rod pigment) (36,37). All light levels fall within the safety guidelines set out in British Standard BS EN 15004-2 (2007). The adapting light will cover 8° visual angle in the test eye, centred 5° inferior to fixation.

All lights will then be extinguished, and the test stimulus will be presented to the same inferior location on the retina. The test stimulus will be a spot of light ~2° in diameter (peak wavelength of 505nm). During the test, the participant will be required to respond by pressing a button on their keypad each time they see the stimulus. The stimulus will be presented for 200ms every 2-3 seconds. Individual thresholds will be established using a 3 down 1 up staircase procedure (0.3 log units v 0.1 log units), where threshold will be defined as the first time the stimulus is seen on an ascending staircase. Threshold will be monitored continuously for up to 40 minutes after cessation of the adapting light.

The researcher will use a standard Early Treatment of Diabetic Retinopathy Study (ETDRS) (38) letter chart to measure the best corrected visual acuity (BCVA; number of letters seen at 4m) in each eye and binocularly with distance refractive error in place (determined by the researcher on the day of the visit). The room lighting will be extinguished during the procedure with the luminance of the test chart between 80 and 320 $cd.m^{-2}$.

The researcher will use a standard Pelli-Robson letter chart to measure the contrast sensitivity in both eyes and binocularly with habitual spectacle correction in place(39), plus an additional +0.75DS in each eye to account for the 1m viewing distance. The room will be illuminated and the luminance of the test chart between 60 and 120 $cd.m^{-2}$. Letter by letter scoring will be used, whereby each correct letter is scored as 0.05 log CS, not including the first triplet which has a value of 0.00 logCS.

In order to attribute a Beckman AMD severity grade to each participant (26), the researcher will use a colour retinal camera (Topcon Triton DRI-OCT at Cardiff; Topcon Maestro at City) to obtain ~45° photographs of the posterior pole from both eyes, in conjunction with SD-OCT imaging to exclude the presence of neovascular changes. SD-OCT imaging will also be used to obtain measurements of total retinal thickness and RPE-Bruch's complex thickness averaged in 9 sub fields of the ETDRS grid. The researcher will use the Heidelberg Spectralis to obtain a 20°x20° (6x6mm) square scan comprising 512x97 pixels with central fixation and automatic real time mean (ART) set at 8 Frames. Automatic retinal layer segmentation will be performed by the inbuilt software, and retinal layer thickness obtained from each of the 9 ETDRS subfields. Near infra-red confocal scanning laser ophthalmoscopy

imaging (NIR cSLO) will also be carried out using the same device, in order to provide additional information regarding retinal features present, including reticular pseudodrusen (RPD). NIR imaging will also enable a provisional assessment of eligibility prior to dark adaptometry testing in the first baseline visit, as colour fundus photography must be performed after dark adaptometry to ensure that the camera flash does not influence the state of retinal adaptation.

The LLQ 32-item questionnaire, designed to highlight visual deficits associated with AMD, will be conducted to provide a patient reported outcome measure regarding visual function in low light levels (24,40). The questions will be administered orally by the researcher and the individual responses recorded. In this questionnaire, scores are combined across items into 6 subscale categories (Driving; Extreme lighting; Mobility; Emotional distress; General dim lighting; Peripheral vision for interpretation.

In order to assess global retinal function, parameters of the full field electroretinogram (ERG) will be recorded. This will be carried out according to the standard testing procedure described by the International Society for Clinical electrophysiology of Vision (ISCEV) guidelines (25). The researcher will conduct an electroretinography assessment using an Espion E3 Electroretinography System (Diagnosys, UK). Three standard skin electrodes (10mm Ag-AgCL disc electrodes) will be positioned (one reference electrode placed temporal to each eye and a ground electrode placed on the forehead), with a Dawson-Trick-Litzkow (DTL) fibre conjunctival electrode acting as active electrode for each eye. Prior to testing, the impedance for each electrode will be checked and recorded, an impedance value greater than 5 KΩ will lead to replacement of the electrode(s) with high impedance. Participants will undergo the standard ISCEV ERG protocol for both eyes which includes the following individual tests: Dark-adapted 0.01 ERG; Dark-adapted 3 ERG; Dark-adapted 10 ERG; Light-adapted 3.0 ERG; Light-adapted 30 Hz flicker ERG (25). A data file will be generated containing the raw data, the software will also automatically calculate the wave peak time (ms) and amplitude (μV) outcome measures based on the participant responses.

Rod and cone optical density and visual pigment synthesis rates will be determined using imaging retinal densitometry (IRD; Cardiff site only). The IRD device used in this sub-study is a unique experimental device that is currently based at Cardiff

University. It uses retinal imaging to produce topographical maps of photopigment density. The device is also able to record the photopigment density in real time, allowing it to map the regeneration rate of photopigments following exposure to a bright light.

The researcher will prepare the participant for IRD by allowing their eyes to dark adapt in a dimly lit room (<1.5 log scot td) for 30 minutes. A standard IRD recording procedure will be undertaken as described in Margrain et al. 2020 (33). This, briefly, involves the recording of: 1) a dark adapted image sequence for 1 minute, 2) an assessment of back scatter (30s), 3) a high resolution fundus photograph, 4) a long duration photopigment bleach with a retinal illuminance of 6.1 log scot td, lasting 120s, which bleaches approximately 95% cone and 98% rod visual pigment and 5) a bleach recovery recording that lasts 10 minutes.

All researchers will be trained by local PIs in obtaining all outcome measures until they are deemed to be sufficiently proficient to achieve high quality data collection. Prior to the start of the trial, a training day with researchers from both sites together will take place to ensure consistency between sites.

Plans to promote participant retention and complete follow-up

In the interest of promoting participant retention, close communication between the sites and participants will be fostered. This will include monthly phone calls for the duration of the treatment, and phone calls and appointment letters to remind about upcoming visits. Travel expenses will be refunded to facilitate travel to the site for visits, as will the expenses of any carer who accompanies the participant. Additionally, appointments for the next visit will be made at the end of each participant visit to site to ensure that this has been scheduled ahead of time. As an additional incentive, a £50 shopping voucher will be provided to each participant at the end of the trial, to thank them for their time and contribution.

If a participant wishes to stop taking part in the trial, if possible, they will be seen one last time for the OCT assessments to look at the retina to check for any adverse reaction. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, we will continue to collect information about them for as long as the reaction lasts. If the participant progresses to late AMD, they will be withdrawn from trial treatment. They will still be encouraged to attend all follow-up appointments

although in these circumstances, it is recognised that it would be unlikely for the participant to undertake the dark adaptometry and IRD assessments due to their visual limitations.

Data management

eCRFs and raw clinical data will be stored on a secure encrypted database system accessed by an institutional password and complying with the General Data Protection Regulation (GDPR) 2016 standards. Inbuilt validations will check for missing or unusual values (range checks) and consistency over time. The CTR will send reminders for any overdue data. Raw source data for dark adaptometry, retinal imaging and retinal densitometry will be stored on a secure encrypted research data server at Cardiff University.

Confidentiality

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Participants will be given a unique participant ID to identify them in all assessment and treatment data. No individual will be identifiable in any publications that result from the trial, or in any data shared with other researchers. All personally identifiable data will be securely stored on a password protected encrypted server (paper copies will be locked in filing cabinets in rooms with restricted access) and will only be accessible by members of the research team where strictly necessary. Data will be stored for a minimum of 15 years and will be registered in accordance with the Data protection Act 2018 and the General Data Protection Regulation 2016. The data custodian for this trial is Cardiff University. Access to de-identified participant level-data is available on request to Centre for Trial Research along with a code book for the dataset. The CTR at Cardiff University will be provided with copies of consent forms for monitoring purposes and to enable audit and regulatory inspections

Statistical methods

Statistical methods for primary and secondary outcomes

The primary analysis will be descriptive. Feasibility outcomes (proportion, recruited and retained at each time points) as well as levels of data completeness will be

tabulated for each follow-up time point with confidence intervals.

For secondary outcomes, baseline data will be tabulated for all randomised participants by arm and overall. Available case follow-up data at 4 and 12 months will be similarly tabulated by arm and overall. Unadjusted differences between arms will be calculated for continuous normally distributed outcomes and presented with 95% confidence intervals at each time point. Transformation to normality will be considered for non-normally distributed outcome data. Adjustment for demographic factors will be considered where baseline imbalance is present for age and gender. Cross-tabulations will be provided for categorical outcomes. In line with the feasibility design and objectives of the trial, no hypothesis tests will be carried out and no p-values will be calculated or presented.

Rod cone break time is a key clinical effectiveness outcome for the trial. Estimates of observed effects on rod cone break time will be provided by group at baseline and follow-up. Preliminary data from a single arm study in 6 participants with AMD (unpublished data) demonstrated a reduction in rod cone break time from 22.8 (5.8SD) min to 17.42 (4.9SD) min, 2 months after starting to take triterpenoid saponins. This suggested a large within group effect size of 0.92. Increasing the sample size from 6 to 30 participants on treatment and including a randomised control group means that a between group 95% confidence interval around a treatment estimate can be provided in this trial. Mean and variance data will be used to determine sample size in a future fully powered trial if effect estimates from this feasibility trial are clinically relevant.

A more detailed statistical analysis plan will be produced by the trial statistician during trial set-up and recruitment. The analysis plan will be completed and signed off before the trial database is completed and locked. All analyses will be carried out blind to allocation. There will be no interim analyses or subgroup analyses. In line with the feasibility objectives of this trial, we will report protocol non-adherence and levels of missing data but no adjustments will be required since we are not estimating treatment effects.

Statistical methods for the Clinical Sub-Study

Thirty participants will be recruited at the Cardiff site to establish means and variance of rod and cone visual pigment synthesis rates collected at 3 timepoints (baseline, 4

months and 12 months). The recruitment, withdrawal and loss to follow-up and data collection procedures will follow those in the main SAMADI trial protocol. The statistical analysis will look for associations between IRD metrics (continuous data) and disease stage (an ordinal measure) using the Kendall rank correlation coefficient. The relationship between IRD metrics and psychophysically measured dark adaptation (continuous data) will be evaluated using linear regression analysis. Treatment effects (outcome at 12 and 4 months - baseline) will be calculated (means) and the uncertainty estimated (95% confidence intervals will be established). There will be no interim analysis. Numbers will be insufficient for subgroup analyses.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

The Project Team (PT) will meet fortnightly and will include the CI, Trial Manager, Data Manager, Statistician and other research staff directly employed to the trial. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Trial Management Group (TMG).

The TMG will consist of the CIs, Co-Applicants, Collaborators, Patient Representatives, Trial Manager, Data Manager and Trial Statistician. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents. They will also advise on the promotion and running of the trial and deal with any issues that arise. The group will normally meet monthly throughout the course of the trial. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

A Trial Steering Committee (TSC), consisting of an independent chair, and three other independent members including a participant representative, will meet at least annually. The first meeting will be before the trial commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The Trial Manager and Trial Statistician will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

Composition of the data monitoring committee, its role and reporting structure

To monitor accumulating data on safety and any trial intervention benefit, an independent data monitoring committee (IDMC) will be established. The committee will consist of an independent chair and two/three other independent members, including a statistician and an independent pharmacist. The first meeting will take place before the trial commences to review the protocol. The main role of the IDMC is to review the data periodically and make recommendations to the TSC. IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter.

Adverse event reporting and harms relating to the clinical trial

All serious adverse events (SAEs) will be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR pharmacovigilance and Safety Specialist. SAEs will be reported up to and including the 12 month visit time point. The medically qualified doctor, delegated by the PI, will perform the seriousness and causality assessments on behalf of the site and record this on the SAE form.

The Investigators' Brochure for this particular triterpenoid saponin formulation indicates that "rare cases of mild insomnia, diarrhoea, nausea and vomiting, headache and gastric discomfort (dyspepsia) have been reported [in some clinical trials] but were only transitory". If these events occur in this trial, they will be reported on the relevant follow-up eCRF and forwarded to the CTR in the normal timeframes for CRFs. They will not require reporting as SAEs unless considered to be serious, in which case they will be classed as unexpected and will be reported as an SAE. For the purposes of this trial the onset of neovascular AMD, and any SAE thought to be related to the dilating eye drops will also be considered SAEs.

The delegated appropriately qualified individual will assess each serious adverse reaction (SAR) with reference to the Reference Safety Information (RSI) to perform the assessment of expectedness. The CTR may request additional information relating to any SAEs/SARs and the site will provide as much information as is available to them to resolve these queries. The site will also report SAEs to their own

organisation in accordance with local practice.

Once central review has occurred, the site will send the SAE to the participant's GP practice and the GP practice will be asked to record the information in the participant's medical records. If the SAE is thought to be related to the dilating eye drops, this will also be reported by the site to the Medicines and Healthcare Products Regulatory Authority (MHRA) using the yellow card scheme (https://yellowcard.mhra.gov.uk/).

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting Suspected Unexpected Severe Adverse Reactions (SUSARs) and other SARs to the regulatory authorities (MHRA and relevant ethics committees) and to AltRegen Co Ltd. SUSARs which are fatal or life-threatening will be reported to the MHRA and Research Ethics Committee (REC) within 7 calendar days of receipt at the CTR, with any follow-up information to be reported within a further 8 calendar days. SUSARs that are not fatal or life-threatening will be reported to the MHRA and REC within 15 days of receipt at the CTR, with any additional, relevant information to be reported within a further 15 days.

To enable processing of a SAR in this masked trial, expectedness will be assessed initially using the assumption that the IMP has been given to the trial participant. If it is assessed as unexpected as per the RSI, the participant thought to be experiencing a SUSAR will be unmasked by the CTR safety specialists prior to reporting to the MHRA and REC. If after unmasking, it is evident that the trial participant received the placebo, this event will not require expedited reporting to the MHRA and REC, unless in the opinion of one of the delegated medically qualified doctors the event was related to the placebo. A list of all SARs (expected and unexpected) will be reported annually to the MHRA, REC, trial sponsor and AltRegen Co Ltd. in the form of a Development Safety Update Report, which must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs as they occur throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report.

Any urgent safety measure relating to this trial will be notified to the MHRA and

Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. AltRegen Co Ltd. will also be informed in line with these timelines.

Adverse event reporting and harms relating to the Clinical Sub-Study

The clinical sub-study taking place at the Cardiff site involves the evaluation of a non CE marked device, an imaging retinal densitometer. Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618) and Annex X of the Medical Devices Directive 93/42 require all adverse events to be fully recorded and all SAEs to be reported immediately notified to the MHRA.

All device deficiencies will be recorded on the site Device Deficiency log and forwarded to the CTR Safety Team within 48 hours, or 24 hours if the Device Deficiency resulted in, or might have led to, an SAE. The CTR Safety Team will inform the CI and the manufacturer within 48 hours. If the deficiency led to an SAE or might have led to an SAE, it will be reported to MHRA Devices in line with the SAE reporting timelines below. All device deficiencies will be summarised and sent to MHRA Devices in the periodic report.

All adverse events that occur during the use of the IRD will be recorded by the site on the participant's Clinical Investigation AE form and forwarded to the CTR trial team in the normal timeframes for CRFs. A report of the AE will be provided to the Chief Investigator and the manufacturer in a timely manner.

If the adverse event fulfils the definition of a SAE, the event will be reported to the CTR Safety team within 24 hours of knowledge of the event. Once reported to the CTR, if the SAE is thought to be related to the IRD, the delegated appropriately qualified individual will assess the event to determine if it is anticipated or unanticipated. If the SAE occurred during the use of the IRD, regardless of whether the SAE is considered to be device related or not, the CTR must report the SAE to the CI, Manufacturer and MHRA devices by email within 2 or 7 days, depending on the severity of the event. Once central review has occurred, the site will inform the participant's GP practice and the GP practice will be asked to record the information in the participant's medical records. If an Adverse Device Event is defined as serious then the device must be quarantined as soon as possible by the site.

Frequency and plans for auditing trial conduct

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the SAMADI trial. The source data for this trial are the consent forms, eCRFs, summary of medical history provided by the GP and assessment files taken from the optometry equipment, all of which will be uploaded onto the trial database, which can be monitored centrally. The IMP accountability documentation can also be sent to the CTR for central monitoring. Therefore, central monitoring, with triggered site monitoring, will be used in this trial and are fully documented in the trial monitoring plan.

Investigators will agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from central monitoring and triggered on-site monitoring will be shared with the Sponsor, CI, PI & TMG.

The trial is subject to inspection by the MHRA as the regulatory body. The trial may also be inspected and audited by Cardiff University under their remit as Sponsor. The site will inform the CTR of any MHRA inspections.

Important protocol amendments will be communicated to all sites by the CTR throughout the trial, and will also be presented to the TMC and the TSC.

Feasibility benchmarking criteria for progression to a Phase III trial

As this is a Phase II trial, benchmarking criteria will be applied to the study feasibility outcomes to determine whether it is appropriate to progress to a Phase III trial. Table 3 summarises these feasibility benchmarks.

Measure	Green: Proceed to Phase III RCT	Amber: Proceed to Phase III RCT with changes	Red: Do not proceed to Phase III RCT
Consent rate for screening and trial Consent rate per month/per site	2+	1-1.9	<1
Randomisation rate Randomisation rate per month/per site	2+	1-1.9	<1
Conversion rate eligible to consented and registered % eligible who consent and are registered over those pre-screened	≥90%	≥30% & <90%	<30%
Conversion rate registered to randomised following full screening (e.g. medical report review): % registered (following consent) who are subsequently randomised	≥90%	≥50% & <90%	<50%
Retention % retained in study and complete measures at 4/12 month follow-up over those randomised	≥90%	≥50% & <90%	<50%
Adherence % adhere to treatment	Participants taking IMP for a minimum of 75% of days	Participants taking IMP for a minimum between 75% and 50% of days	Participants taking IMP for a minimum less than 50% of days
Feasibility of the eligibility assessment process % of eligible patients over the number screened	≥90%	≥30% & <90%	<30%
Feasibility of collecting outcome data % of completed forms returned over the number of forms expected at each timepoint (baseline, 4 months and 12 months).	≥90%	≥50% & <90%	<50%

Table 3: Feasibility benchmarks to determine progression to Phase III RCT

Dissemination plans

With respect to publications, standard principles in accordance with the policy of the International Committee of Medical Journal Editors will be followed. The CI will co-ordinate dissemination and writing of data from the main trial. All publications and presentations relating to the trial will be authorised by the Trial Management Group in accordance with the trial publication policy. The results of the trial will be disseminated regardless of the magnitude or direction of effect, via a full report to the funder and in peer-reviewed journal publications. Results will be published in

accordance with the CONSORT statement minimum set of recommendations for reporting the results of randomised trials (41). The trial results will also be presented at an international conference, such as the Association for Research in Vision and Ophthalmology annual meeting in May 2027.

Discussion

This protocol has been reported in accordance with the guidelines of the SPIRIT statement of recommendations for reporting the protocol of a randomised trial (41). This Phase II feasibility trial will provide important information about all aspects of trial feasibility for future trial design. This will include information about the recruitment and retention of participants, eligibility assessment, acceptability of the intervention and adverse event rates, as well as adherence to recommended usage, collection of outcome data. Secondary outcomes will provide data regarding the standard deviation of the clinical measures, and the potential size of any treatment effect. This information will be crucial in the design of a future phase III trial.

Trial status

The trial is currently recruiting participants. Recruitment began in March 2025, and is expected by be completed by January 2026.

Abbreviations

AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual acuity
CI	Chief Investigator
CS	Contrast Sensitivity
CTR	Centre for Trials Research (Cardiff University)
eCRF	electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
GDPR	General Data Protection Regulation
IDMC	Independent Data Management Committee
ISCEV	International Society for Clinical Electrophysiology of Vision
ISRCTN	International Standard Randomised Controlled Trial Number
IMP	Investigative Medicinal Product
IRB	Institutional Review Board
IRD	Imaging Retinal Densitometry
LOCS	Lens Opacities Classification System
LLQ	Low Luminance Questionnaire
MA	Marketing Authorisation
MHRA	Medicine and Healthcare products Regulatory Agency
NC	Nuclear Colour
NHS	National Health Service
NIHR	National Institute for Health and care Research
NIR cSLO	Near Infra-red confocal scanning laser ophthalmoscopy
NO	Nuclear Opalescence
P	Posterior sub-capsular cataract
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PROM	Participant reported outcome measure
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD-OCT	Spectral Domain Optical Coherence Tomography

SUSAR	Suspected Unexpected Serious Adverse Reactions
TMG	Trial Management Group
TSC	Trial Steering Committee

Declarations

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Authors' contributions

AB and AW contributed equally to the drafting of this paper. TM was the chief investigator at the inception of the trial; he conceived the study and oversaw the protocol development. MV is the current chief investigator; she reviewed the medical safety aspects of the protocol and contributed to reviewing the draft document. AB and AW are principal investigators at City St George's, University of London and Cardiff University, respectively. AW and IC led the drafting of the first version of the protocol. AB contributed to the protocol development and drafted the manuscript for publication. KP, VS and MG are research optometrists, who contributed to the development of the protocol. RL is the senior trial manager at Cardiff CTR; she contributed to the development of the protocol. SB was trial manager at Cardiff CTR at the time of manuscript submission and she led the integration of protocol amendments. RP is the trial statistician; SJ was the data analyst for the trial in the developmental stage; CN was the Academic Lead for Public Involvement and

Engagement – all of whom contributed to the development of the protocol, and reviewed the draft manuscript for publication. YL contributed to the initiation of the project and the protocol development, particularly with respect to the development and delivery of the IMP.

All authors read and approved the final manuscript.

Funding and role of funder and sponsor

The trial is funded by AltRegen Co. Ltd. It has been adopted to the National Institute for Health Research (NIHR) portfolio.

The funder has contributed to the protocol development for this study, but will have no role in the collection, management, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. As Sponsor, Cardiff University, is responsible for ensuring that there are proper arrangements in place to initiate, manage, monitor and finance the study. They do not have a direct role in the analysis and interpretation of data, the report writing or publication.

Availability of data and materials

The PI organisations will allow access to source data/documents as required for audits and regulatory inspections. The Sponsor (Cardiff University) owns the dataset and is the data controller. The data set will be shared with third parties subject to due diligence and a relevant data sharing agreement being in place. Data sharing requests should be sent to the sponsor via the Centre for Trials Research to SAMADI@cardiff.ac.uk.

Ethics approval and consent to participate

This study has approval from a research ethics committee (REC) that is legally recognised by the United Kingdom Ethics Committee Authority for review and approval. The REC reference is 24/NI/0019. Additional approvals have been obtained from the Medicines and Healthcare products Regulatory Agency (MHRA), reference CTA 21323/0062/001-0001. Written, informed consent to participate will be obtained from all participants.

Consent for publication

No personally identifiable data will be published.

Competing interests

AB has a consultancy agreement with Boehringer Ingelheim. Yunhee Lee is employed by AltRegen Co. Ltd. No other authors have any declarations of interest.

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