OZDRY

Clinical Study Report

Title Page:

Study Title (short)	OZDRY
Study Title (full)	A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema
Name of test drug/investigational product	700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)
Indication studied	Diabetic macular oedema
Name of the sponsor	Moorfields Eye Hospital NHS Foundation Trust, 162, City Road, London EC1V 2PD
Sponsor Representative	Ms Maria Hassard, Moorfields Eye Hospital, Tel 0207 566 2819 Fax 0207 608 6925
Chief Investigator	Prof Sobha Sivaprasad, Consultant Ophthalmologist, Moorfields Eye Hospital
Funder	Allergan Pharmaceuticals
Clinical trials.gov	NCT01892163
EudraCT No	2012-003661-17
Version and date of protocol	Protocol SS01 Version 7.0 dated 07-03-2014
Development phase of study	Phase 3
Study initiation date (First patient first visit)	5th February 2013
Study completion date (Last patient last vist)	10th November 2014
GCP Statement	This study was conducted in compliance with Good Clinical Practice (GCP) guidelines including the archiving of essential documents.
Date of report	06/11/2015

1. Contents

2. Synopsis

OBJECTIVE:
To compare the clinical effectiveness and safety of 5-monthly fixed dosing versus pro-re-nata (PRN) Ozurdex treatment in patients with refractory diabetic macular oedema (DMO).

DESIGN:
Prospective, multicentre, randomized active-controlled non-inferiority clinical trial.

SETTING:
Medical Retina Clinics in 5 UK National Health Service hospitals.

PARTICIPANTS:
100 patients who attended Medical Retina Clinics for management of centre involving refractory DMO.

INTERVENTIONS:
Participants were randomized 1:1 to either 5-monthly fixed dosing or optical coherence tomography (OCT) - guided PRN regimen of Ozurdex therapy for DMO. Data were collected on best-corrected visual acuity (BCVA), patient reported outcome measures (PROM), macular thickness and morphology, diabetic retinopathy status, number of injections and adverse events from baseline for a period of 12 months.

MAIN OUTCOME MEASURES:
The primary outcome was the difference between arms in change in BCVA from baseline to 12 months. The pre-specified non-inferiority margin was 5 ETDRS letters. Key secondary outcomes included change in PROM scores; change in macular thickness; change in retinopathy and macular morphology and safety profile.

RESULTS:
The mean change in BCVA was +1.48 (SD 14.8) in the fixed arm versus -0.17 (SD 13.1) in the PRN arm, with adjusted effect estimate +0.97, 90% confidence interval (-4.01, +5.95), p=0.02 (per protocol analysis) and the conclusions of the ITT analysis were primarily supportive, -0.34 (-5.49, 4.81) p=0.07, but sensitive to an alternative assumption on missing data +0.28
(-4.72, 5.27) p = 0.04.

CONCLUSIONS:
The mean change in BCVA with five monthly fixed dosing of Ozurdex was non-inferior to OCT guided PRN Ozurdex therapy for refractory DME based on a per protocol analysis

3. List of abbreviations

ADA	American Diabetic Association
BCVA	Best Corrected Visual Acuity
CRF	Case Report Form
CST	Central Sub-field Thickness
DEX PS DDS	Dexamethasone Posterior Segment Drug Delivery system
DMC	Data Monitoring Committee
DMO	Diabetic Macular Oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
FAZ	Foveal Avascular Zone
FFA	Fundus Fluorescein Angiography
GCP	Good Clinical Practice
HbA1c	Glycosylated Haemoglobin
IOP	Intraocular Pressure
ITT	Intention to Treat
KCL	King's College London
LOCF	Last Observation Carried Forward
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
OCT	Optical Coherence Tomography
OU	Ocular Uterque, both eyes
PP	Per Protocol
PRN	Pro-re-nata
PROM	Patient reported outcome measures
RetDQoL	Diabetic Retinopathy Quality of Life
RetTSQ	Retinopathy Treatment Satisfaction Questionnaire
SD	Standard Deviation
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VFQ 25	Visual Function Questionnaire
WHO	World Health Organisation

4. Ethics

The study protocol was approved by the UK Collaborative Research Ethics Committee (12/LO/1534). The principles of Good Clinical Practice were adhered throughout in accordance with the Declaration of Helsinki. Please see Appendix I for ethics approval and Appendix II for MHRA approval.

5. Patient information and consent

The Principal Investigator and co-investigators who were on the delegation log took the informed consent at the screening visit. Informed consent was obtained before any trial-related procedures were done. The person taking consent was GCP trained, suitably qualified and experienced. A minimum interval of 24 hours was given to patients between the patient information leaflet being given and informed consent being taken.

Adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study were explained to the patient before signing the consent form. The investigator explained to the patients that they were under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. A copy of the signed Informed Consent was given to the participant. The original signed form was retained at the study site.

Please see appendix III for the Patient information sheet and appendix IV for the Consent form for this study

6. Investigators and study administrative structure

This study was conducted across five sites with Prof. Sobha Sivaprasad as the Chief Investigator and one principal investigator for each site. Statistician services were provided by Moorfields eye hospital, while the randomization and database services were provided by Kings College London. The details of all these personnel with the trial steering committee and data monitoring committee are shown in appendix V and the curriculum vitae of the chief investigator is in appendix VI

7. Introduction

Centre-involving diabetic macular oedema (DMO) is a leading cause of moderate visual loss in diabetes.[1]The visual outcome and vision related quality of life of people with centre-involving DMO have significantly improved with the initiation of inhibitors of vascular endothelial growth factor (VEGF).[2,3] However, many patients still need frequent and multiple injections of anti-VEGF and up to 50% of treated patients do not achieve long term resolution of DMO.[4,5]

Therefore, there is a significant unmet need for alternative interventions for refractory DMO.[6]

Intravitreal steroids were the first class of intravitreal drugs that were evaluated for the treatment of this condition and remain a promising treatment modality for people with DMO due to both its anti-inflammatory and anti-vascular permeability effects. [7,8] The Ozurdex (Allergan Inc.) drug delivery system is a sustained-release formulation for posterior-segment delivery of 700 micrograms dexamethasone. The Phase 3 MEAD study that evaluated the role of 6 monthly pro-re-nata (PRN) dosing of Ozurdex for DMO reported that 22% of patients improved ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at the end of 3 years.[9] Another trial that compared the combination of Ozurdex and laser therapy versus laser therapy (PLACID) in DMO reported that when Ozurdex was given at baseline and then optionally at month 6 or 9, the proportion of subjects with a 10 letter gain at all time points up to 12 months was significantly higher in laser treatment only. However, the study also reported that to obtain a sustained effect of Ozurdex, the treatment should be repeated at shorter intervals than every 6 months based on the changes observed in macular thickness on optical coherence tomography (OCT) and visual acuity.[10] The OCTOME study reported that the maximum treatment response of the drug occurred at 12 weeks before the effect wore off gradually. Therefore, a more frequent dosing between 16 and 20 weeks may be necessary to avoid the undulating effects on macular thickness and visual acuity.[11] A 16 weekly PRN dosing evaluated in the BEVORDEX study reported that 41% of the patients in the study improved 10 or more letters.[12] However, the OZLASE study reported that mandated Ozurdex injections at baseline and 16 weeks followed by PRN dosing based on stringent re-treatment criteria resulted in dose-dependent cataract formation or progression that confounded the potential for visual benefit (in press). Therefore, a great deal of uncertainty still exists on the optimal dosing of Ozurdex to adopt for patients with DMO.

The objective of this study was to find the best dosing schedule that would provide optimal visual benefit with minimal burden on patients and hospital services. Therefore, we compared the risk-benefit ratio of 5-monthly fixed dosing versus OCT guided PRN dosing of Ozurdex in centre-involving refractory DMO whilst keeping the treatment burden to a minimum. The primary objective was to evaluate whether 5-monthly fixed dosing of 700 µg Ozurdex is non-inferior to OCT- guided PRN dosing in patients with DMO. Our null hypothesis was that the change in best corrected visual acuity (BCVA) between baseline and 12 months is more than 5 ETDRS letters lower in the fixed dosing (investigative) arm than in the OCT guided PRN dosing (standard) arm, to be assessed after adjusting for baseline BCVA and study site. The alternative hypothesis is that fixed dosing is non-inferior to OCT guided PRN dosing in terms of the change in BCVA between baseline and 12 months, being no lower in the fixed dosing arm than the PRN dosing arm by a non-inferiority margin of 5 ETDRS letters.

8. Study Objectives

This study was conducted to evaluate whether 5 monthly fixed dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) is as efficacious as OCT-guided PRN dosing in terms of mean change in visual acuity in patients with refractory DMO. It also evaluated between these two arms, patient reported outcomes, safety of dosing and anatomical changes in patients with refractory DMO

9. Investigational Plan

9.1 Overall Study Design and Plan

This is a multicentre, open-label, randomized 12-month study aimed to compare the efficacy of 5 monthly fixed dosing (intervention arm) versus OCT-guided PRN dosing (standard arm) of intravitreal Ozurdex in patients with refractory DMO defined as central sub-field thickness (CST) exceeding 300µm despite laser and/or antiVEGF treatments.

After informed consent, patients underwent baseline examinations of best corrected visual acuity (BCVA), optical coherence tomography (OCT), autofluorescence, and 4 field retina colour photos and fundus fluorescein angiography (FFA) and completed questionnaires on quality of life and treatment satisfaction. 100 eligible participants were randomized in a 1:1 ratio to be in one of the treatment arms of the study. Primary outcome assessors (optometrists and OCT technicians) were masked to treatment allocation.

Fixed dosing arm had mandatory doses of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) at baseline and thereafter every 5 months unless criteria for deferred treatment was met. Participants in the OCT-guided PRN dosing arm were treated at baseline and then at any visit thereafter if CST was more than 300 µm but the interval between consecutive injections was not less than 16 weeks. Efficacy measures included BCVA in ETDRS letters; central retinal thickness (CRT) and number of treatments. Patient reported outcomes were recorded using visual function questionnaires VFQ25, RetDQoL and treatment response questionnaire using RetTSQ. Safety measures include increased IOP, cataract surgery and other adverse events

Please see appendix VII for the study protocol, appendix VIII for the summary of protocol amendments and appendix IX for case report forms.

Please refer to Tables 1 and 2 for schedules of study assessments in both arms.

Table 1 - Standard: PRN dosing arm

	Baseline (Day 0)	Treatment Of OZURDEX	4 M (120 days)	5 M (150 days)	6 M (180 days)	7 M (210 days)	8 M (240 days)	9 M (270 days)	10 M (300 days)	11 M (330 days)	12 M (360 days)
Assessment Window		(+ 7 days from baseline)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)
Informed Consent	x										
Blood Pressure	x										X
HbA1c	x										X
Pregnancy test (females of child bearing potential)	x										X
BCVA (refraction 0, 12 months)	x		X	X	x	x	x	x	x	x	X
Ophthalmic examination	x		X	X	x	x	x	x	x	x	X
IOP	x		X	X	x	x	x	x	x	x	X
LOCS II	x		X	X	x	x	x	x	x	x	X
4 field stereo photos	x										X
OCT	x		X	X	x	x	x	x	x	x	X
Autofluorescence	x										X
Fluorescein angiography	x										X
VFQ-25	x										X
RetDQoL	x										X
RetTSQ	x										X
**Ozurdex injection*	x	X	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	
ADVERSE EVENTS			X	X	x	x	x	x	x	x	X
Post injection safety monitoring call		X (+5days)	X (+5days)	x (+5days)	X (+5day)	X (+5day)	x (+5day)	X (+5day)	x (+5day)	x (+5day)	

* Treatment of Ozurdex injection should be given no later than +7 days after baseline assessments

If Treatment with Ozurdex is performed, the next visit will be at 4 month.

(+/- = if reinjection criteria met) A post-injection VA and IOP check should be done 1 week and 8 weeks after any Ozurdex injection. Visit window after baseline is ± 7 days

Table 2 - Intervention: Fixed Dosing Arm

	Baseline (Day 0)	Treatment of OZURDEX	5 M (150 days)	10 M (300 days)	12 M (360 days)
Assessment Window		(+ 7 days from baseline)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)
Informed Consent	x				
Blood Pressure	x				x
HbA1c	x				x
Pregnancy test (females of child bearing potential)	x				x
BCVA (refraction 0, 12 months)	x		x	x	x
Ophthalmic examination	x		x	x	x
IOP	x		x	x	x
LOCS II	x		x	x	x
4 field stereo photos	x				x
OCT	x		x	x	x
Autofluorescence	x				x
Fluorescein angiography	x				x
VFQ-25	x				x
RetDQoL	x				x
RetTSQ	x				x
Ozurdex injection	x	X	x	x	
ADVERSE EVENTS			x	x	x
Post injection safety monitoring call		x (+5days)	x (+5days)	x (+5days)	x (+5days)

*Treatment of Ozurdex injection should be given no later than +7 days after baseline assessments
A post-injection VA and IOP check should be done 1 week and 8 weeks after any Ozurdex injection.
Visit window after baseline is ± 7 days

9.2 Selection of study population

9.2.1 Inclusion criteria

1. Subjects of either sex aged 18 years or over
2. Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following will be considered to be sufficient evidence that diabetes is present:
    - Current regular use of insulin for the treatment of diabetes
    - Current regular use of oral anti-hyperglycaemic agents for the treatment of diabetes
3. Documented diabetes by ADA and/or WHO criteria Best corrected visual acuity in the study eye between ≥34 and ≤73 ETDRS letters tested as per protocol at baseline attributable to DMO.
4. On clinical exam at baseline in the study eye, retinal thickening due to diabetic macular oedema involving the centre of the macula and OCT central subfield > 300 microns (Spectralis) despite previous therapy.
5. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs.
6. Ability to return for study visits
7. Visual acuity in fellow eye ≥ 2/60
8. Ability to give informed consent throughout the duration of the study

If both eyes were eligible the eye with the better visual acuity was entered into the randomisation process, unless patient decided otherwise.

9.2.2 Exclusion criteria

The following exclusions apply to the study eye only (i.e. they may be present for the non-study eye)

1. Macular ischaemia (FAZ > 1000μm in diameter or severe perifoveal intercapillary loss on fluorescein angiography.
2. Macular oedema is considered to be due to a cause other than diabetic macular oedema. An eye should not be considered eligible if:
    - the macular oedema is considered to be related to cataract extraction or
    - clinical exam and/or OCT suggest that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal membrane) is the primary cause of the macular oedema.
3. Co-existent ocular disease: An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular oedema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, non-retinal conditions, such as amblyopia).

4. An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study (e.g. vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass syndrome, etc).
5. A substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e., cataract would be reducing acuity to 6/12 or worse if eye was otherwise normal).
6. History of treatment for DMO with peribulbar or intravitreal steroids in the study eye in the past 6 months.
7. History of macular laser in study eye in the last 3 months.
8. History of antiVEGF therapy within the last 1 month.
9. Active proliferative diabetic retinopathy or rubeosis in the study eye at baseline. (Stable and treated proliferative diabetic retinopathy may be included).
10. A condition that, in the opinion of the investigator, would preclude participation in the study.
11. A past medical history of significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant
12. Major surgery within 28 days prior to randomisation or major surgery planned during the next 12 months at baseline. Major surgery is defined as a surgical procedure that is more extensive than fine needle biopsy/aspiration, placement of a central venous access device, removal/biopsy of a skin lesion, or placement of a peripheral venous catheter.
13. Participation in an investigational trial within 30 days of randomisation that involved treatment with any drug that has not received regulatory approval at the time of study entry. Note: subjects cannot receive another investigational drug while participating in the study.
14. Pregnant or lactating women or women intending to become pregnant within the study period.
15. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 3 months or anticipated within the next 6 months following randomisation.
16. Aphakia
17. A diagnosis of glaucoma which in the opinion of a glaucoma specialist is at high risk of progression or ocular hypertension requiring at least one topical medication.
18. History of vitrectomy in study eye.
19. Examination evidence of external ocular infection, including conjunctivitis, chalazion, or severe blepharitis. If treated these subjects can be included.
20. Known allergy to fluorescein dye or to any component of the study drug.
21. Fertile male unwilling to use contraception for the duration of the study

Contraceptive advice to women of child-bearing age and fertile males
Women of child-bearing potential were advised to use contraception for the duration of the study. They were advised not to deliberately become pregnant during the trial and use contraception for 3 months after the study concludes. Fertile males were advised to use contraception for the duration of the trial.

9.2.3 Removal of patients from therapy or assessments

Patients were discontinued from taking the study drug if:

- The patient developed a clinically significant medical condition that prevents continuous treatment within the study.
- The patient developed a potentially life threatening condition.
- The patient moved out of the area and is unable to return for assessments.
- Women who became pregnant during the trial

Withdrawn patients were not replaced. Reasons for withdrawal and any follow-up information were collected with timing.

9.3 Treatments

9.3.1 Treatments administered

The Ozurdex (Allergan Inc.) drug delivery system is a sustained-release formulation for posterior-segment delivery of dexamethasone, made of a polylacticglycolic acid (PLGA) matrix. It received its market authorisation (EU/1/10/638/001) on 27th July 2010 as Ozurdex 700 micrograms intravitreal implant in applicator.

9.3.2 Identity of investigational products

Ozurdex will be supplied by Allergan, principal place of business being Castlebar Road, Westport, County Mayo, Ireland. The hospital pharmacy will be responsible for drug accountability. All used/unused IMP(s) that are dispensed should be returned to the trial pharmacist. They will be responsible for maintaining & updating the drug accountability log, in each hospital pharmacy file. Drug destruction will be conducted, once agreed by the sponsor and in accordance to local pharmacy practice, and this will be documented on the drug destruction log in the hospital pharmacy file.

9.3.3 Method of assigning patients to treatment groups

Subjects were randomised 1:1 into either the fixed dosing or the PRN dosing schedule of Ozurdex therapy via a bespoke web based randomisation system hosted at the King's CTU. Patients were randomised at the level of the individual, using the method of block randomisation with randomly varying block sizes, stratified by study site. The use of randomly varying block sizes ensured that treatment allocation does not become deterministic towards the end of

each block and thus will protect pre-randomisation allocation concealment. If both eyes were eligible, the eye with the better visual acuity was entered into the randomisation process, unless patient decides otherwise.

Please refer to appendix X for patient identifier and treatment assigned according to individual site.

9.3.4 Selection and timing of dose

All patients received baseline Ozurdex injection. Intravitreal Ozurdex injections were performed under local anaesthesia and post-injection topical antibiotics were used. Further Ozurdex injections in each arm were performed according to protocol-defined retreatment criteria. In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points. In the standard arm, participants were seen at baseline, 4 months and then monthly to assess the need for re-treatment. If the participants in standard arm were re-treated at any point, the next visit was after 4 months. In addition, safety visits were done at 1 and 8 weeks after any Ozurdex injection in either treatment arms. If there was any safety concern in the opinion of the investigator, more frequent optional post-injection assessment visits were allowed.

Re-treatment with Ozurdex was indicated if the CST on OCT exceeded 300 µm and the intraocular pressure (IOP) was ≤ 25 mmHg. If the IOP was between 26 and 30mmHg, topical anti-glaucoma eye drops were given before treatment with Ozurdex at the same sitting. If the IOP recorded was 30 mmHg or more, anti-glaucoma eye drops were given and the patient was reviewed a week later and Ozurdex was injected only if the IOP had reduced to less than 30mmHg. Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation. The total duration of study participation was 12 months.

9.3.5 Blinding/Masking

Primary outcome assessors (optometrists and OCT technicians) were masked to treatment allocation. The visual acuity examiners received the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be refracted, but with no previous subject records or case report forms by which the subject treatment arm could be identified. Similarly, the OCT technicians received the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined.

The patients and clinicians who administered the study treatment and those who

performed the safety evaluations were not masked to the treatment arms. The subjects were advised at enrolment that they must not discuss the study arm they were in with the OCT or Visual Acuity examiner.

9.3.6 Prior and concomitant therapy

1. All medication(s)/treatment(s) excluding intravitreal antiVEGF, periocular and intravitreal steroids and macular laser treatment were permitted during the trial period in the study eye of the patients.
2. The need to initiate anti-glaucoma medications or surgery if IOP ≥ 26 mmHg. Consultation with glaucoma specialist was to be considered.
3. Cataract surgery for visually significant cataract during the study period was left to the discretion of the investigator. A masked grader determined whether the cataract was visually significant before cataract surgery was planned. Steroid and antibiotic eye drops pre-and post cataract surgery were permitted.
4. Non-study eye treatment with steroids, laser and antiVEGF agents was allowed
5. Pan retinal photocoagulation for retinal neovascularisation in both study and non-study eye was permitted

9.3.7 Treatment compliance

Patients were treated in the trials unit during the scheduled visits. So non-compliance for treatment after attending the unit was very unlikely, unless there were any contraindications to treatment. Non- compliance with the patient attending the study visit was a possibility.

9.4 Efficacy and safety variables

9.4.1 Efficacy and safety measures assessed and flowchart

The following assessments were performed during the study visit. For schedule (flow chart) of these assessments please see Tables 1 and2 in Section 9.1

Informed Consent
Inclusion/exclusion criteria
Medical and Ophthalmic history
Concomitant medications/procedures
Blood Pressure
Pregnancy test (urine) – required for female subjects of childbearing potential
HbA1c
BCVA (manifest refraction) (OU)

IOP measurement (OU)
OCT (OU)
Autofluorescence (OU)
Biomicroscopy (includes lens grading) (OU)
4 field retinal photographs
Fluorescein angiography (OU)
Patient-reported outcomes assessment NEI-VFQ-25,[13] RetDQoL,[14] RetTSQ[15]
Randomisation
700 µg DEX PS DDS placement
Query for adverse events
Post injection safety monitoring call <5 days after DEX PS DDS placement

9.4.1.1 Protocol for Measuring Best Corrected Visual Acuity

Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation. The visual acuity examiners will receive the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be refracted, but with no previous subject records or case report forms by which the subject treatment arm could be identified. The subjects will be advised at enrolment that they must not discuss the study arm they are in with the Visual Acuity examiner.

Refracted best corrected visual acuity is performed at baseline, and 12 months in all subjects in both eyes. Open aperture best corrected visual acuity is recorded in both eyes at all other assessments. VA is always measured in the study eye first, then the fellow eye. If cataract surgery is done during the study, refraction should be repeated in the next trial visit and this new refraction should be used in all follow-up visits until 12 months when refraction will be repeated in both eyes.

Initial VA Measurement:

At the baseline visit, initial VA is measured, whilst the subject is wearing his/her own distance glasses or unaided (if subject doesn't have distance glasses), using ETDRS Chart R. At all follow-up visits refraction found during the previous study refraction will be used. The fellow eye is lightly patched with a tissue. If the initial acuity is less than 20/200 refraction should occur at 1 metre.

Retinoscopy

Retinoscopy should be performed using a light / duochrome chart at 6m.

Subjective Refraction

Subjective refraction should be carried out according to the methods routinely employed by the Optometry Department locally. The subjective refraction is performed at 4m using a ETDRS chart with the room lights off.

Final VA Measurement

VA in the study eye first is always measured first, then the fellow eye. The subject is instructed that the chart contains letters only and no numbers. If the subject forgets this during the course of the examination, they should be reminded that the chart contains no numbers and asked for a letter instead of the number. The subject is advised that there are 5 letters on each line, and that they should attempt to read the line from left to right. The examiner must not point at any letters or read any letters out loud during the test. It is acceptable to briefly point at a line, should the subject have difficulty finding the next line. The subject should be instructed to read the letters slowly, about one letter per second. The subject should be encouraged to guess any letters that are difficult to read, and be instructed to make a definite decision. If the subject is unable to identify a certain letter they should tell the examiner that they are moving on to the next letter along the line. If the subject incorrectly identifies a letter and then proceeds to read the next letter, s/he cannot go back and correct the mistake later. It is permissible to allow correction as long as the subject has not started to read the next letter aloud. The subject should be asked (and encouraged) to move on to the next line, as long as they manage to correctly identify at least one letter on the previous line.

With the subject wearing the best correction in the trial frame, the eye not being tested is occluded with a standard occluder in the trial frame, or with a tissue/patch behind the frame, if the subject moves his/her head a lot to use eccentric fixation.
Following refraction the best VA's are measured at 4m using ETDRS Chart 1 for the right eye and Chart 2 for the left eye. During the VA measurements the room lights need to be switched off.
The subject is asked to look at the smallest line they can read on the ETDRS. Follow the instructions for recording the final ETDRS-score and VA outlined below.

ETDRS Score

Each letter correctly identified is circled on the visual acuity form. Any letters read incorrectly are deleted, and letters, for which no guess has been made, are left unmarked. Each correct letter scores one point. The total for each line is recorded in the right-hand column (max.5), and the scores for each line added at the bottom. If the score is 20 or more, then 30 points are added automatically

and the final VA score is recorded. If the total score is less than 20, then the acuity should be tested at 1m. The chart is moved so that it is exactly 1m from the subject. Before testing at 1m, +0.75DS should be added to the sphere in the back cell of the trial frame. If the subject feels that this makes their vision worse, then it should be removed again. Only the first six lines are read at 1m, giving a maximum score of 30. The approximate Snellen equivalent is also recorded in feet. The Acuity recorded is the smallest line with 1 or no error

Testing for Count Fingers

If the subject's VA is so poor that s/he cannot correctly identify any letters on the chart when tested at one meter, then test for Count Fingers. The eye not being tested should be completely occluded with a patch. A light must be shone from behind the subject's head at the examiner's hand. The examiner holds the hand two feet in front of the subject's face and presents an arbitrary number of fingers in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the subject correctly identifies 3 of the 5 presentations, then count fingers vision is noted. If not, then the subject must be tested for hand movements.

Testing for Hand Movements

The eye not being tested is occluded with a patch. A light must be shone from behind the subject's head at the examiner's hand. The examiner's hand should be moved two feet in front of the subject with all fingers spread out. The hand should be moved either horizontally or vertically at a constant speed of approx. one back and forth movement per second. The subject is asked to watch the examiner's hand and respond to the question "in which direction is my hand moving?" The examiner should not explain that it will be moving either from side to side or up and down! Correct answers at four out of five presentations suggest that hand movement vision is present. If not, then light perception should be tested for.

Testing for Light Perception

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope should be focused at 1meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the eye at least four times, and the subject should be asked to respond when they see the light. If the examiner is convinced that the subject perceives light, vision should be recorded as "Light Perception". If not, vision should be recorded as "No Light Perception".

9.4.1.2 LOCS II Lens Grading[16] Protocol

The presence and severity of nuclear, cortical and posterior subcapsular lens opacities will be measured during slit lamp examination using standardized photographs and the Lens Opacities Classification System II (LOCS II)

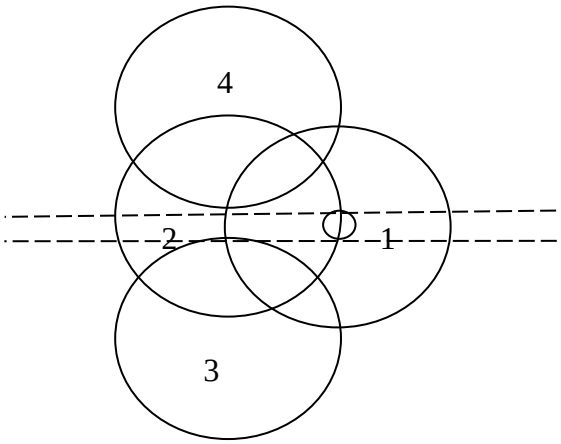
Pupils should be dilated
Slit Lamp examination with 10X Magnification
The appropriate codes are used separately for right and left eye

Nuclear Colour	
NC0	<N1 standard
NCI	Similar to N1standard
NCII	>N1 standard
Nuclear Standard	
N0	Clear Nucleus
NI	Early degree of nuclear opacification
NII	Moderately advance nuclear opacification
NIII	Advanced nuclear opacification and browning
Cortical Standard	
C0	Clear lens devoid of aggregated dots flecks vacuoles and waterclefts
Ctr	Minimal degree of cortical opacification and or mini spoke formation
CI	More extensive opacification with small minispokes
CII	Cortical spoking that obscures more than 2 full quadrants
CIII	Opacification that obscures about 50% of the intrapupillary zone
CIV	Advanced opacification filling about 90% of the intrapupillary zone
Posterior subcapsular cataract	
P0	Clear posterior capsule
P1	Cataract filling about 3% of the area of the posterior capsule
PII	About 30% opacification of the area of the posterior capsule
PIII	About 50% opacification of the area of the posterior capsule

9.4.1.3 4 Field Colour Fundus Photography Protocol

Aim: To grade the degree of retinopathy in all subjects at baseline and final follow-up at 12 months.
Method: 4 stereo photographs must be obtained as follows: (diagram 1)

Diagram 1: 4 field retinal photography



1. Centred on the disc with the temporal border on the macula
2. Centred on the macula with the nasal border over the centre of the disc.
3. Directly inferior to the macula with the inferior border in line with the superior edge of the disc.
4. Directly superior to the macula with the superior border in line with the inferior edge of the disc.

SAMPLING TIME
4 field stereo photos will be taken at baseline and at exit (12months)

MINIMAL CRITERIA
Fields 1 and 2 must be in focus

GRADING
To be performed by the investigator.

9.4.1.4 Fundus Fluorescein Angiography (FFA) Protocol

FFA was performed in all subjects at baseline to determine the degree of macular ischaemia and therefore study suitability. FFA was repeated in all subjects at 12 months to assess the degree of macular ischaemia in terms of greatest linear diameter of FAZ, area of the FAZ and degree of perifoveal capillary dropout. Minimal Criteria for acceptable FFA quality were that early

phase angiography must be performed to allow grading of macular ischaemia. The macula must be in focus. For digital capture the following fields are preferable. Field 2 - Macula: Centre the macula at the intersection of the cross hairs in the ocular. It is important that good even illumination is used at all times and that the flash settings are kept at the correct levels to ensure this.

The timing for the procedure is as follows: -

1. Before the injection of the fluorescein dye
2. Position camera on F2 of eye to be treated (index eye) prior to injection.
3. 5ml of fluorescein is injected rapidly (in less than 5secs if possible).

Early or Transit Phase

1. The 1st photograph of F2 of the index eye is taken at the start of the injection and the 2nd at the end of the injection. The purpose of this is to document the time taken to inject the dye.
2. 15-30 sec (F2 index eye): - Take a rapid series of about 10-16 exposures at intervals of about 1 to 2 seconds.

Mid Phase

1. 30 - 45 seconds: F2 of the index eye
2. 50 seconds - 1 min: F2 of the fellow eye
3. 2 min: F2 of the index and fellow eye
4. 2½-3 min: F2 of index eye

Late Phase

- 5 min: F2 of index eye and fellow eye

9.4.1.5 Grading Macular Ischaemia Protocol

Grading of macular ischaemia is based on an early phase / mid-phase photograph.
It is determined by 3 grading systems. These are the maximum diameter of the foveal avascular zone, area of the foveal avascular zone and degree of perifoveal capillary dropout according to the ETDRS standard photo of moderate capillary loss.

DIAMETER OF THE FAZ
The greatest linear dimension of the foveal avascular zone will be documented with the measuring tool on the Topcon system. This will be done by the study investigators.

AREA OF FAZ
This is measured by hand drawing a line around the edge of the foveal avascular zone and using the automated area measuring tool on the Topcon software to calculate the FAZ area.

ETDRS PERIFOVEAL CAPILLARY DROPOUT
Intercapillary distance will be judged against standard ETDRS photograph of moderate perifoveal capillary dropout.
Normal : normal perifoveal intercapillary distance
Questionable : slightly abnormal perifoveal intercapillary distance
Mild : definitely abnormal but better than moderate standard ETDRS photograph
Moderate : equal to moderate ETDRS standard photograph
Severe : worse than moderate ETDRS standard photograph.

9.4.1.6 Spectral Domain OCT Protocol

Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation. The OCT technicians will receive the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined. Optical Coherence Tomography (OCT) will be assessed on both eyes at baseline and month 12. Only study eye will be assessed at every other visit. These assessments will be performed by an OCT certified clinical trial unit technician. OCT imaging will be performed using the Spectralis OCT machine.

Investigators and the OCT grading technicians will use OCT to diagnose and to monitor presence or absence of significant macular oedema. The macular thickness measurement determines whether subjects randomised to Ozurdex PRN dosing therapy receive a further injection that day; this occurs if CST ≥ 300µm in the central ETDRS subfield.

OCT parameters will include:

Resolution mode:	High Speed
ART:	≥20 (the setting is 24)
Pattern:	(49 scans, 20°, 120µ separation)
Centred:	Anatomical fovea

9.4.1.7 Procedure for intravitreal Ozurdex Injection

1. Injection is performed under sterile conditions in a designated treatment room. The procedure will be explained to the subject who will then lie supine. Prior to injection, a preloaded injection of Ozurdex will be supplied from Pharmacy Clinical Trial stock.

2. A local anaesthetic injection (2% lignocaine) will be given to the bulbar conjunctiva.
3. The eye is disinfected. This involves scrubbing the eyelids, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. It is important to ensure that the eyelid margins and lashes are swabbed, procedure is performed in a systematic fashion and that povidone iodide is used to irrigate the conjunctival sac.
4. The skin is then dried and a drape applied and a lid speculum is inserted to retract the eyelids
5. The subject is instructed to direct their eyes upward and medially. The preferred site of injection is inferotemporally. The conjunctiva and sclera can be held with a tooth forceps to minimise risk of the eye moving during the injection.
6. With calipers, 4.0mm is measured posterior to the limbus in the phakic patent and 3.5mm in the pseudophakic subject. Ozurdex is then injected at this site, through the pars plana in the inferotemporal quadrant, into the vitreous cavity, aiming towards the centre of the globe. The injection should be delivered slowly. The needle should then be removed slowly to ensure the implant is in the eye. If possible a sterile cotton tip applicator should be placed on the injection site to minimise reflux.
7. A drop of topical antibiotic is placed in the fornix at the end of the procedure. The subject will be monitored with a finger count test by the injecting physician immediately (within 90 seconds) after injection of Ozurdex.
8. The IOP is checked after 30 minutes and if the IOP is raised (> 30mmHg) it is repeated every 15 minutes until it has fallen to < 30mmHg. If the IOP remains persistently elevated (>30mmHg) it can be treated with systemic or topical medication at the Investigators' discretion.
9. Following injection, topical antibiotic is instilled into the eye 4 times a day for 4 days and the subject is advised to contact the Clinical Trials Unit immediately should any symptoms suggestive of infection develop after intravitreal injection.

9.4.2 Primary outcome measure

Change in BCVA ETDRS letter score between baseline and 12 months, in the two study arms (after adjusting for baseline BCVA ETDRS letter score and study site).

9.4.3 Secondary outcome measure

1. Proportion of patients with an improvement (defined as a gain of 10 ETDRS letters or more) in BCVA between baseline and 12 months, in the two study arms
2. Proportion of patients with a stabilization (defined as a loss of less than 15 ETDRS letters) of BCVA between baseline and 12 months, in the two study arms
3. Distribution of BCVA change between baseline and 12 months, in the two study arms, broken down by the following 5 categories:
    a) ≥15 letters improvement,
    b) ≥5 and <15 letters improvement,
    c) no change (i.e. ≥4 and <5 letters,
    d) ≥5 and <15 letters worsening and
    e) ≥15 letters worsening.
4. Change in central retinal thickness (CRT) between baseline and 12 months, in the two study arms
5. Change in morphological characteristics of DMO on OCT between baseline and 12 months, in the two study arms
6. Proportion of patients with a decrease in leakage on fundus fluorescein angiography (FFA), foveal avascular zone (FAZ) parameters and ETDRS grade of retinopathy between baseline and 12 months, in the two study arms
7. Total number of treatments in the two study arms
8. Change in each domain and composite scores of the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), Retinopathy Treatment Satisfaction Questionnaire (RetTSQ) and Retinopathy-Dependent Quality of Life questionnaire (RetDQoL), between baseline and 12 months, in the two study arms
9. Total number of adverse events in the two study arms

9.5 Data Quality Assurance

Case Report Forms with data from each visit was entered by the Data Entry Team within 7 days of a patient visit to the study database. Once entered, data is automatically uploaded to the database server within KCL.

Data range, consistency and missing data checks will automatically be performed at data entry to the trial database system. These will be monitored by an independent monitor who will report any major issues to the Trial Manager. Due to the extensive level of monitoring in place, double data entry will not be performed. However, all primary outcome

data entered onto the study database will be source data verified to check for transcription errors.

Additional range, consistency and missing data checks will be performed, as appropriate, by the Statistician at the time of analysis (and when the datasets for analysis are constructed). All variables will be examined for unusual, outlying, unlabelled or inconsistent values. Any problems with trial data will be queried with the Trial Manager and Principle Investigator. As far as possible, data queries will be resolved; although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist.

Please see the following table for data management plan

1. Data entry time scale	7days after patient visits
2. Data chase for missing data	Fortnightly by data officer at Moorfields
3. Data queries sent to sight	Fortnightly by data officer at Moorfields
4. Query resolution from sites	Site given 7 days to resolve queries
5. Query resolutions added to trial database	Site given 7 days to update query on trial database
6. Monitoring frequency	1x green light, 2x site visit, 1x close out.
7. Data extraction	For DMC meetings
8. Consistency checks	Monthly by trial manager
9. Medical Data Review	Monitoring

9.6 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.6.1 Statistical and analytical plans

9.6.1.1 Analysis principles

1. Recruitment, randomisation and follow-up:

This will be summarised by study arm in a CONSORT flow-diagram. This will provide details on the number of eligible patients for the trial, the number consenting and the number randomised. It will also provide a breakdown of the number randomised to each study arm, the number receiving the intended treatment, the number completing the study protocol, and the number analysed for the primary outcome.

2. Intent-to-treat (ITT) or per-protocol (PP) populations:

The primary analyses will be conducted by both ITT and PP, as these are considered as equally important in a non-inferiority trial. All other analyses will be performed by ITT.

The trial ITT population comprises all randomised patients regardless of eligibility (inclusion/exclusion) error, post randomisation withdrawal and whether the correct study treatments were received, or other interventions received. The PP population is defined as the subset of the ITT population that met the eligibility criteria and received the randomised treatment in accordance with the protocol).

3. Significance levels of tests:

The primary outcome analysis will use a one-sided p-value of 0.05, with a one-sided 95% confidence interval (or equivalently a two-sided 90% confidence interval), in accordance with a non-inferiority design. All other statistical tests will use a two-sided p-value of 0.05, with a two-sided 95% confidence interval.

4. Baseline comparability:

Baseline characteristics will be summarised by study arm and overall. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. A tabulation of concomitant medications by study arm will also be presented.

5. Follow-up and losses to follow-up: missing data:

It is inevitable that some patients will be lost to follow-up. Sample size estimation assumed 10% of patients would not provide a 12 month evaluable outcome. If data are missing for any patients, reasons for missing may be important and these will be examined using logistic regression of covariates (i.e. study arm, baseline BCVA and variables listed in Table 1) and on an indicator of missing. A sensitivity analysis will only be considered if the level of missing data is greater than 10%.

6. Adjustment for design factors:

Since randomisation was stratified by baseline BCVA (<54 or ≥54 ETDRS letters) and study site, analysis of the primary outcome will also be adjusted for baseline BCVA and study site.

7. Masking in the analysis stage:

The statistician will be masked to treatment status up until the time of database lock.

9.6.1.2 Planned analysis

Primary endpoint analyses:

The primary outcome is the difference in mean change in baseline best corrected ETDRS visual acuity (BCVA) letter score at 12 months between the two study arms, after adjusting for baseline BCVA and study site. The mean and standard deviation will be reported by study arm. The treatment effect estimate will be reported as the difference in means, with a two-sided 90% confidence interval. Non inferiority will be assessed by comparing the two-sided 90% confidence interval for the difference in means to the inferiority margin. Analysis will be on an ITT basis and supported by a PP analysis. For the purposes of the PP analysis, a protocol deviation will be defined as any patient who either did not meet the required inclusion-exclusion criteria and/or was not treated in accordance with the re-treatment criteria as outlined in the trial protocol

Secondary endpoint analyses:

Summary statistics will be provided for all secondary outcome measures by study arm. Summary measures will be mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Treatment effect estimates will be reported as differences in means for continuous (approximate) normal data, differences in medians for non-normally distributed data and as odds ratios (using logistic regression) for binary data, after adjusting for baseline BCVA, study site and the respective baseline covariate, where appropriate. Effect estimates will be presented with a two-sided 95% confidence interval.

9.6.2 Determination of Sample size

This study was designed as a non-inferiority trial with the non-inferiority limit for the difference between study arms in the mean change in visual acuity at 12 months of 5 ETDRS letters lower under fixed dosing, assessed after adjusting for baseline BCVA ETDRS letter score and study site. If there is no statistically significant difference in the change in BCVA ETDRS letter score between baseline and 12 months, in the populations represented by two study arms, a sample size of 90 patients was required to be 83% certain that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) would be above the non-inferiority limit of 5 letters, assuming that the common standard deviation (SD) was 9 letters. The SD is based on the results of the Ranibizumab (RESOLVE) study.[17] The non-inferiority margin of 5 ETDRS letters is based on the CATT study (in which it is recognised as a commonly accepted margin) and the results of the PLACID study. Allowing for 10% missing data, 100 patients were randomized (i.e. 50 patients per study arm).

9.7 Changes in the conduct of the study or planned analyses

At the request of the Data Monitoring Committee (DMC), an additional post hoc sensitivity analysis with alternative missing data assumptions was then conducted for the ITT population. This used in place of available case analysis, a last observation carried forward (LOCF) analysis approach, which carried forward data in these three patients who did not provide primary outcome data at 12 months.

Sensitivity analysis was conducted to assess the effect of having cataract surgery during the study on the primary outcome. This was restricted to those included in the primary analysis and was done by replacing the final visual acuity measurement with the last available visual acuity measurement before surgery and repeating the primary analysis.

A related within subgroup analysis of the primary outcome was performed on patients who were pseudophakic at baseline. This provided an unbiased but less precise estimate of the treatment effect in this subgroup which is free from any cataract-related issues.

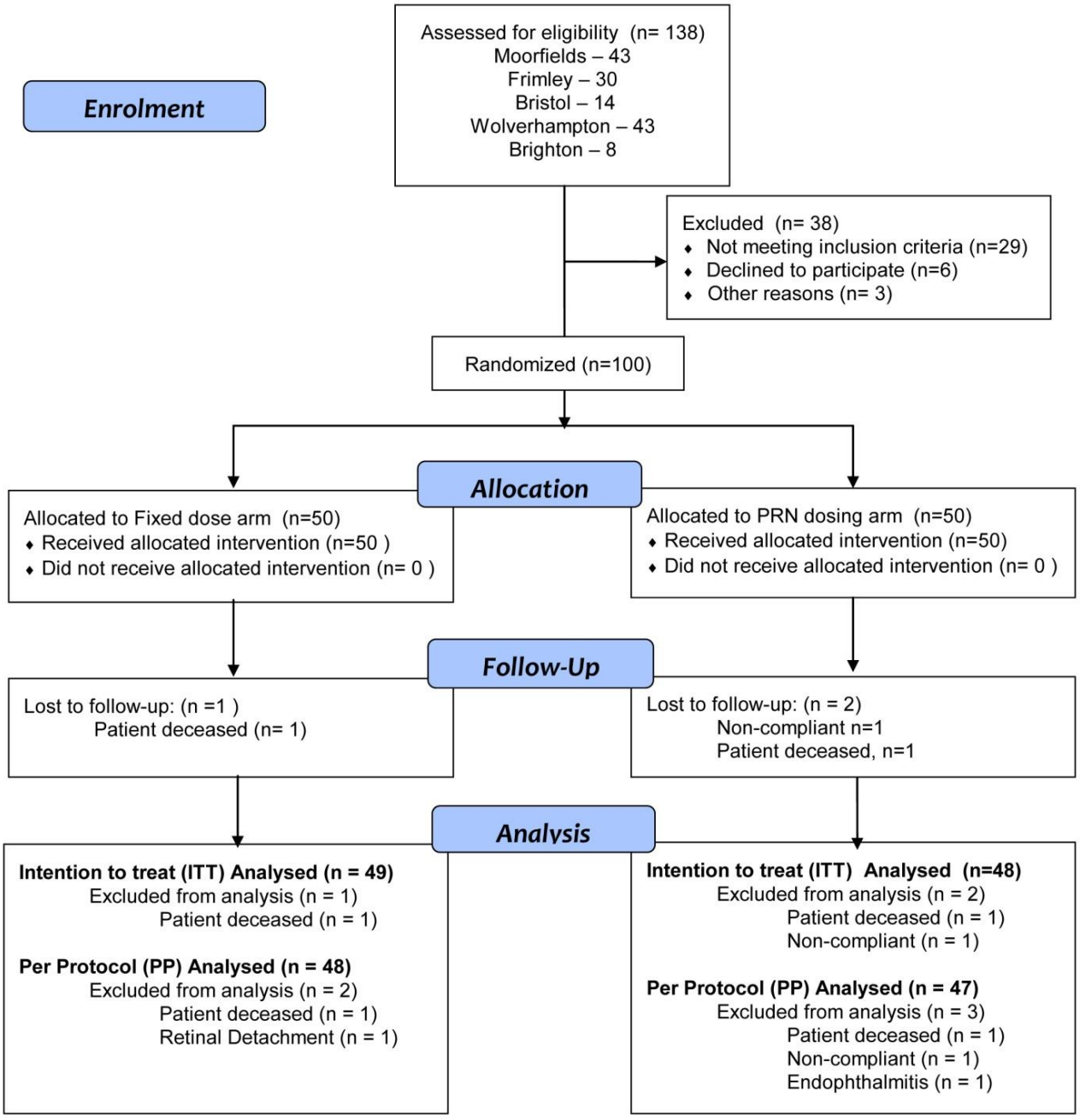
10. Study Patients

10.1 Disposition of patients

A total of 100 patients were enrolled from February 2013 to November 2014 and randomized to study treatment across 5 sites. All recruited patients received the baseline Ozurdex injection and 49/50 (98%) in the fixed arm and 48/50 (96%) in the PRN arm completed the study providing primary outcome data (ITT). For the per protocol primary analysis, 2/50 (4%) patients and 3/50 (6%) patients were excluded from fixed and PRN arm respectively due to protocol deviations. The 3 patients excluded in the ITT were also excluded in the PP analysis.

The following CONSORT diagram describes the flow of participants at each stage.

CONSORT diagram



10.2 Protocol deviations

Inclusion and exclusion criteria not met, but enrolled in the study		1 patient
Declined treatment following endophthalmitis		1 patient
Did not attend main study appointments		7 visits
Did not attend safety visits		10 visits
Attended outside window for main study appointments		16 visits
Attended outside window for safety visits		33 visits
Safety phone calls not done		54 visits
Study related procedures not done due to machine / patient	Auto Fluorescence	16 visits
	FFA	8 visits
	HbA1c	8 visits

Apart from the above deviations, there was an unmasking issue with optometrists at Moorfields Eye Hospital, until 7th January 2014. Once the issue was identified, root cause analysis was done. It highlighted the fact that visual acuity testing procedures and masking procedures were on different pages in the protocol. Immediate corrective actions were taken and masking was implemented. Based on the fact that the optometrists were not aware of randomisation arm at baseline and that the optometrists were masked to assess the 12 months outcome measure and none of the patients had exited the trial during this period of unmasking, this issue did not affect the data integrity of OZDRY study. This was discussed both at the Research monitoring committee and the data monitoring committee.

11. Efficacy Evaluation

11.1 Data sets analysed

All recruited patients (100) received the baseline Ozurdex injection and 49/50 (98%) in the fixed arm and 48/50 (96%) in the PRN arm completed the study providing primary outcome data (ITT). For the per protocol primary analysis, 2/50 (4%) patients and 3/50 (6%) patients were excluded from fixed and PRN arm respectively due to protocol deviations. The 3 patients excluded in the ITT were also excluded in the PP analysis.

11.2 Demographics and other Baseline Characteristics

Table 3 - Non-Ocular Baseline Characteristics by Study Arm

	Fixed dosing	PRN dosing
Males, n (%) [N]	40 (80) [50]	34 (68) [50]
Age (years), mean (SD) [N]	63.8 (11.1) [50]	65.4 (9.8) [50]
Ethnicity [N]	[50]	[50]
White / Caucasian, n (%)	34 (68)	35 (70)
Black or African, n (%)	5 (10)	5 (10)
South Asian, n (%)	10 (20)	8 (16)
Other, n (%)	1 (2)	2 (4)
Diabetes [N]	[50]	[50]
Type 1, n (%)	7(14)	2 (4)
Type 2 on insulin, n (%)	22 (44)	22 (44)
Type 2 on tablets, n (%)	21 (42)	26 (52)
Duration of Diabetes (months) median (IQR) [N]	192 (112, 255) [50]	196 (124, 249) [50]
HbA1c (%), mean (SD) [N]	8.1 (1.4) [50]	7.7 (1.3) [50]
Systolic BP (mmHg), mean (SD) [N]	148.5 (20.5) [50]	142.8 (20.5) [50]
Diastolic BP (mmHg), mean (SD) [N]	79.3 (9.8) [50]	77.7 (10.8) [50]

PRN= pro-re-nata; n = number of patients; N = total number of patients; SD = standard deviation; IQR = interquartile range; BP = blood pressure; HbA1c = glycated haemoglobin

Table 4 - Ocular Baseline Characteristics by Study Arm

	Fixed dosing	PRN dosing
ETDRS BCVA, mean (SD) [N]	57.5 (9.5) [50]	61.2 (8.6) [50]
Duration of DMO (months), median (IQR) [N]	35.5 (15.0, 51.0) [50]	37.0 (18.0, 48.0) [50]
Prior treatments		
Macular laser therapy, n (%) [N]	46 (92) [50]	48 (96) [50]
Pan-retinal photocoagulation, n (%) [N]	14 (28) [50]	8 (16) [50]
Intravitreal Anti-VEGF, n (%) [N]	17 (34) [50]	17 (34) [50]
Intravitreal steroids, n (%) [N]	5 (10) [50]	3 (6) [50]
OCT findings		
CRT (µm), mean (SD) [N]	479.8 (128.4) [50]	466.7 (144.1) [50]
CST (µm), mean (SD) [N]	472.4 (113.5) [50]	467.9 (126.4) [50]
Macular volume (mm^3), mean (SD) [N]	10.0 (2.5) [50]	10.4 (2.1) [50]
Lens status		
Pseudophakic, n (%) [N]	16 (32) [50]	11 (22) [50]
Phakic, n (%) [N]	34 (68) [50]	39 (78) [50]
Presence of cataract, n (%) [N]	24 (70.6) [34]	31 (79.5) [39]
ETDRS grade of retinopathy		
Mild NPDR, n (%) [N]	16 (32) [50]	17 (34) [50]
Moderate NPDR, n (%) [N]	17 (34) [50]	21 (42) [50]
Severe NPDR, n (%) [N]	5 (10) [50]	7 (14) [50]
Treated PDR, n (%) [N]	11 (22) [50]	5 (10) [50]
Not available, n (%) [N]	1 (2) [50]	0 (0) [50]
FFA findings		
FAZ GLD (mm), mean (SD) [N]	808.5 (271.8) [50]	769.0 (190.4) [50]
FAZ Area (mm^2), median (IQR) [N]	0.5 (0.3, 0.7) [49]	0.4 (0.3, 0.6) [50]

PRN= pro-re-nata; n = number of patients; N = total number of patients; SD = standard deviation; IQR = interquartile range; ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; DMO= diabetic macular oedema; CRT = central retinal thickness; CST = central subfield thickness; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; FAZ = foveal avascular zone; GLD = greatest linear dimension; FFA = Fundus fluorescein angiography; VEGF = Vascular endothelial growth factor

11.3 Measurement of treatment compliance

One patient refused further treatment following endophthalmitis in the study eye. As all treatments were carried out during the study visits, non-compliance to treatment was not present. There were 7 study visits missed by the patients. We do not have any data if the patients would have needed treatment if they had attended those visits.

11.4 Efficacy results

11.4.1 Analysis of efficacy

Table 5 shows the ITT analysis (available cases i.e. all patients with at least one exposure to Ozurdex apart from the three without follow-up data at 12 months), the PP analysis and the post-hoc ITT analysis using LOCF of the primary outcome.

Table 5 - Primary Analyses by Study Arm – Efficacy outcome measures

	Fixed dosing ETDRS BCVA, mean (SD) [N]	PRN dosing ETDRS BCVA, mean (SD) [N]	Effect Estimate (two-sided 90% CI)	One-sided P-value
Intention To Treat (ITT) Analysis (available case)				
At 12 months	57.8 (18.5) [49]	61.4 (14.0) [48]	-	-
Change from Baseline*	0.53 (16.1) [49]	0 (13.0) [48]	-0.34 (-5.49, 4.81)	0.07
Per Protocol (PP) Analysis				
At 12 months	58.5 (17.9) [48]	61.1 (14.0) [47]	-	-
Change from Baseline*	1.48 (14.8) [48]	-0.17 (13.1) [47]	0.97 (-4.01, 5.95)	0.02
Post Hoc Last Observation Carried Forward (LOCF) ITT Analysis				
At 12 months	58.0 (18.4) [50]	60.8 (14.2) [50]	-	-
Change from Baseline*	0.52 (15.9) [50]	-0.44 (13.0) [50]	0.28 (-4.72, 5.27)	0.04

ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; N = total number of patients; CI = Confidence interval; PRN = pro-re-nata

* Adjusted for baseline BCVA and study site

Table 6 - Secondary Analyses by Study Arm – Efficacy outcome measures at 12 months from baseline*

		Fixed dosing	PRN dosing	
BCVA (ETDRS letters)		**No of patients, n (%) [N]**	**No of patients, n (%) [N]**	**Odds Ratio**
Improvement	≥ 10 letters	12 (24) [49]	11 (23) [48]	0.82 (0.3, 2.3)
	≥ 15 letters	7 (14) [49]	4 (8) [48]	1.3 (0.33, 5.40)
	≥ 5 and < 15 letters	14 (29) [49]	12 (25) [48]	1.3 (0.50, 3.36)
Stabilization	< 15 letters loss	42 (86) [49]	44 (92) [48]	0.56 (0.15, 2.18)
No Change	≥ -4 and ≤ 4 letters	17 (35) [49]	21 (44) [48]	0.7 (0.3, 1.7)
Worsening	≥ 5 and < 15 letters	4 (8) [49]	7 (15) [48]	0.65 (0.17, 2.60)
	≥ 15 letters	7 (14) [49]	4 (8) [48]	1.76 (0.46, 6.76)
ETDRS grade of retinopathy		**No of patients, n (%) [N]**	**No of patients, n (%) [N]**	**Odds Ratio**
	Mild NPDR	13 (28) [47]	18 (40) [45]	-
	Moderate NPDR	16 (34) [47]	16 (36) [45]	-
	Severe NPDR	6 (13) [47]	4 (9) [45]	-
	Treated PDR	12 (25) [47]	7 (15) [45]	-
PROM - composite score change		**Mean (SD) [N]**	**Mean (SD) [N]**	**Effect Estimate (95% CI)**
	NEI-VFQ-25	3.02 (15.4) [49]	-0.45 (12.2) [47]	3.1 (-2.1, 8.3)
	RetDQoL	-0.38 (1.7) [49]	-0.14 (1.6) [48]	-0.16 (-0.8, 0.5)
	RetTSQ	4.4 (12.7) [49]	3.6 (15.1) [47]	2.7 (-2.3, 7.7)
Central Subfield Thickness		**Mean (SD) [N]**	**Mean (SD) [N]**	**Effect Estimate (95% CI)**
	At 12 months	292.9 (118.9) [47]	372.3 (117.3) [47]	-
	Change from Baseline	-179.9 (172.4) [47]	-90.1 (96.2) [47]	-71.34 (-117.33, -25.34)
Treatment		**Mean (SD) / Median (IQR) [N]**	**Mean (SD) / Median (IQR) [N]**	**Effect Estimate (95% CI)**
	No of injections per patient	2.86 (0.45) / 3 (3, 3) [50]	2.60 (0.70) / 3 (2, 3) [50]	0.26 (0.03, 0.49)

PRN= pro-re-nata; ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; n= number of patients; N = total number of patients; IQR= Interquartile range; CI= Confidence Interval; NPDR= Non-proliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy; PROM= Patient Related Outcome Measures; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire; RetDQoL = Retinopathy Dependent Quality of Life questionnaire; RetTSQ = Retinopathy Treatment Satisfaction Questionnaire

* Adjusted for baseline BCVA and study site

11.4.2 Statistical/ analytical issues

11.4.2.1 Adjustments for Covariates

Summary measures for the baseline characteristics of each arm are presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Treatment effect estimates are reported as differences in means for continuous (approximate) normal data, differences in medians for non-normally distributed data and as odds ratios (using logistic regression) for binary data, after adjusting for baseline BCVA, study site and the respective baseline covariate, where available. Effect estimates are presented with a two-sided 95% confidence interval.

11.4.2.2 Handling of dropouts or missing data

Corresponding ITT and PP 'available case' sample populations were pre-defined as those cases with available primary outcome data. Three patients did not provide primary outcome data at 12 months, one in the fixed arm and two in the PRN arm. This was less than the proportion anticipated to be lost to follow up (10%) confirming the pre-defined available case analysis approach to provide valid treatment effect estimates.

Post hoc sensitivity analysis with alternative missing data assumptions was then conducted for the ITT population. This used in place of available case analysis, a last observation carried forward (LOCF) analysis approach, which carried forward data in these three patients who did not provide primary outcome data at 12 months.

11.4.2.3 Interim analyses and data monitoring

No interim analyses were done for this trial. Data monitoring committee monitored all the adverse and serious adverse events and protocol deviations.

11.4.2.4 Multicentre studies

This study was conducted across 5 sites in the United Kingdom. Analysis of individual centre results was not part of our statistical analysis plan. Although three centres had sufficient number of patients to make such analysis potentially valuable, it was not carried out.

11.4.2.5 Examination of subgroups

Sensitivity analysis was conducted to assess the effect of having cataract surgery during the study on the primary outcome. This was restricted to those included in the primary analysis and was done by replacing the final visual acuity measurement with

the last available visual acuity measurement before surgery and repeating the primary analysis.

A related within subgroup analysis of the primary outcome was performed on patients who were pseudophakic at baseline. This provided an unbiased but less precise estimate of the treatment effect in this subgroup which is free from any cataract-related issues.

Table 7 - Sensitivity analysis to assess the effect of baseline lens status and cataract surgery during the study

	Fixed dosing ETDRS BCVA, mean (SD) [N]	PRN dosing ETDRS BCVA, mean (SD) [N]	Effect estimate (Two-sided 90% CI)	One-sided P-value
ITT Sensitivity Analysis (available case): Cataract Surgery				
At 12 months	57.6 (18.6) [49]	59.8 (14.1) [48]	-	-
Change from Baseline	0.35 (16.0) [49]	-1.65 (13.2) [48]	1.18 (-3.97, 6.34)	0.02
ITT Sensitivity Analysis (available case): Pseudophakic at Baseline				
At 12 months	58.3 (19.9) [15]	63.2 (14.5) [10]	-	-
Change from Baseline	0.53 (14.7) [15]	1.2 (13.6) [10]	0.73 (-11.4, 12.9)	0.2
PP Sensitivity Analysis: Cataract Surgery				
At 12 months	58.3 (18.0) [48]	59.4 (14.0) [47]	-	-
Change from Baseline	1.29 (14.7) [48]	-1.85 (13.2) [47]	2.51 (-2.48, 7.50)	0.007
PP Sensitivity Analysis: Pseudophakic at Baseline				
At 12 months	61 (17.7) [14]	63.2 (14.5) [10]	-	-
Change from Baseline	3.78 (7.8) [14]	1.2 (13.6) [10]	5.81 (-2.44,14.05)	0.02
Post Hoc LOCF ITT Sensitivity Analysis: Cataract Surgery				
At 12 months	57.8 (18.5) [50]	59.2 (14.2) [50]	-	-
Change from Baseline	0.34 (15.8) [50]	-2.02 (13.1) [50]	1.73 (-3.26, 6.72)	0.01
Post Hoc LOCF ITT Sensitivity Analysis: Pseudophakic at Baseline				
At 12 months	59.1 (19.5) [16]	61.9 (14.4) [11]	-	-
Change from Baseline	0.5 (14.2) [16]	0.64 (13.1) [11]	1.22 (-9.51,11.96)	0.16

ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; CI= Confidence Interval; PRN = pro-re-nata; N = total number of patients; LOCF= Last Observation Carried Forward; PP= Per Protocol; ITT= Intention To Treat; PP = per protocol

11.4.3 Drug dose, drug concentration and relationships to response

Both treatment arms received intravitreal Ozurdex 700µg at all treatment time-points. There were no dose modifications in this trial. But the dosing regimen was different for the two arms. In the intervention arm (fixed dosing) mandated dose of intravitreal Ozurdex was given at baseline, 5 and 10 months. In the standard (PRN dosing), re-treatment with Ozurdex was given after the baseline injection if retreatment criteria was met provided the interval between two consecutive injections was more than 16 weeks.

11.4.4 Efficacy conclusions

Primary outcome

The ITT analysis effect estimate was -0.34 (-5.49, 4.81). Whilst this available case analysis interval overlapped the non-inferiority margin by half a letter, this was not seen in either PP analysis or the post-hoc ITT sensitivity analysis based on LOCF. For the ITT (available case), the mean improvement in the visual-acuity letter score in the fixed arm was 0.53 letters and 0 in the PRN arm. Both the PP analysis effect estimate of 0.97, 90% CI (-4.01, 5.95) and the post hoc ITT sensitivity analysis effect estimate of 0.28, 90% CI (-4.72, 5.27) support the claim of non-inferiority between treatment regimens.

Secondary outcomes

The proportion of patients in the fixed arm and PRN arm with ≥15 letters gain were 14% and 8% respectively whilst those who gained 10 or more letters comprised 24% in the fixed arm and 23% in the PRN arm. More patients (43%) gained 5 or more letters in the fixed arm compared to 33% in the PRN arm; however this was not statistically significant. The proportion of patients losing at least15 letters was also greater in the fixed arm (14%) compared to 8% in the PRN arm, albeit not statistically significantly. However, if we consider visual loss as ≥5 letters, both arms showed very similar outcomes of 22% and 23%.

The change at 12 months from baseline in composite score of patient related outcomes such as NEI-VFQ 25 was higher in the fixed arm than in PRN treatment effect estimate 3.1, 95% CI (-2.1, 8.3) although this was not statistically significant. Similarly RetTSQ composite score was higher in the fixed dosing than in the PRN – treatment effect estimate 2.7 95% CI (-2.3, 7.7) - also not statistically significant.

The mean final macular thickness at 12 months was < 300µm (292.9µm) in the fixed arm compared to 372.3µm in the PRN arm. The mean reduction at 12 months from baseline of macular thickness was greater in the fixed arm compared to the PRN arm (-179.9µm vs -90.1µm) with a treatment effect estimate -71.3, 95% CI (-117.3, -

25.3) indicating significantly higher reduction in the fixed arm. It is important to note however that this might reflect the difference in timings of injections between the two treatment arms - 45 of the fixed arm patients had treatments at or after 10 months compared with just 6 of the PRN patients. There were almost 50% more patients with hard exudates in the central 6mm retina in the PRN dosing than in the fixed dosing. The mean number of Ozurdex injections by 12 months was 2.86 in the fixed arm and 2.60 in the PRN arm despite the fact that the fixed arm received 5 monthly dosing whilst the PRN dosing was OCT-guided. The diabetic retinopathy status at 12 months was similar between the dosing arms.

As a final sensitivity analysis, a within subgroup analysis of the primary outcome was also performed on patients who were pseudophakic at baseline. The baseline visual acuity of the pseudophakic group was 58.6 in the fixed arm and 61.3 in the PRN arm. The final mean visual acuities of the pseudophakic group in the fixed arm and PRN were 58.3 and 63.2 respectively. Non-inferiority was only observed in the per protocol sensitivity analysis however the numbers were small (15 vs. 10 pseudophakic patients in the fixed and PRN arm respectively) and as such no firm inferences can be drawn.

12. Safety Evaluation

12.1 Adverse events and serious adverse events (Table 8)

	Fixed	PRN
Total adverse events (n)	**167**	**158**
Ocular adverse events	**136**	**123**
Subconjunctival haemorrhage	83	57
Raised IOP in study eye	8	13
Vitreous haemorrhage	3	3
Cataract progression	5	7
Others	37	43
Non-ocular Adverse Events	**31**	**35**
Total Serious Adverse Events (n)	**9**	**10**
Ocular Serious Adverse Events	**3**	**6**
Retinal detachment	1	0
Cataract surgery in study eye	1	4
Endophthalmitis	0	1
Others	1	1
Non-ocular Serious Adverse Events	**6**	**4**
Death	1	1
Others	5	3

n= total number of events; PRN = pro-re-nata; IOP = intraocular pressure

12.2 Vital signs and clinical laboratory evaluation

There was no difference between arms in changes in systolic and diastolic blood pressure and glycated haemoglobin.

12.3 Safety Conclusions

The proportion of patients that developed with IOP>30mmHg were 20% in the fixed arm and 34% in the PRN arm. Sixty four percent (18/28) patients initiated on topical IOP lowering medication continued on the medication until end of the study and 3 patients required more than 1 topical medication. No patients required surgical intervention for raised IOP in either arm. The topical medications were either initiated at the 8-week visit following a Ozurdex injection or at the next re-treatment visit.

Out of a total of 34 phakic patients in the fixed arm, 27 (79%) showed new onset or progression of cataract based on change in the LOC II grading by at least 1 grade at final visit. These included 3 nuclear, 3 cortical, 8 PSCO and 12 mixed cataract and 1 had cataract surgery. In the PRN arm with 39 phakic patients, 30 (77%) patients showed progression and included 3 nuclear, 6 cortical, 6 PSCO and 11 mixed cataract and 4 had cataract surgery. There was 1 case of retinal detachment in the PRN arm and 1 case of endophthalmitis in the fixed arm and both events were reported as related to the intervention.

13. Discussion and Overall Conclusions

DISCUSSION

The ITT (available case) analysis did not demonstrate non-inferiority. However, the per protocol and the post hoc ITT analysis supported non-inferiority, and it should be observed that the data were more variable than had been anticipated at the point of sample size computation. Trialists do not agree on whether a PP or ITT analysis should be carried out when examining non-inferiority. From a regulatory perspective both populations are of interest and our protocol clearly specified an examination of both. The European Medicines Agency publication states that a non-inferiority trial must show non-inferiority in both the ITT and the PP populations and advice close examination where there are discrepancies. It is for this reason that we conducted a post hoc sensitivity ITT analysis using LOCF for the three subjects who withdrew. This agreed with the PP population and further it should be noted that the original ITT analysis missed the margin by half a letter. In summary therefore we believe that this study lends support to the statement of non-inferiority, i.e. that the results of this trial show that there is no evidence that 5 monthly fixed dosing of Ozurdex is non-inferior to OCT-guided PRN regimen of Ozurdex in patients with refractory DMO in terms of visual acuity at 12 months. Both arms showed similar visual

acuity changes despite more frequent monitoring in the PRN arm. Likewise, both arms showed low mean change in visual acuity at 12 months from baseline despite significant reduction in the central macular thickness, more so in the fixed arm. This may be because cataract progression might have confounded the visual outcomes in both arms or the suggested reduction in macular thickness was transient.

The proportion of patients gaining and losing vision were also similar in the two arms. However, more patients (although not statistically significant) benefited from 5 or more letter gain in the fixed arm. The patient related outcomes were better with the fixed dosing in terms of vision related quality of life and patient satisfaction, although again, not statistically significant with these data. Better results may have been seen because the treatment regime was known to patients in the fixed arm but unknown to the patients until the day of the hospital appointment in the PRN arm. Anecdotal evidence is that patients report considerable distress when there is uncertainty about whether they will be given an injection or not.

About one in five patients also lost ≥5 letters with Ozurdex in both arms and this concurs with previous studies. In the BEVORDEX study, 11% lost 10 or more letters in the Ozurdex arm compared to none in the bevacizumab arm at 12 months. Most anti-VEGF trials report less than 5% of patients losing vision. This may be attributed mainly due to the development of cataract.

The ocular and systemic safety profiles of Ozurdex in both treatment groups of this study were very similar to previous reports with no unexpected events. Although cataract progression and IOP increases are expected complications of corticosteroid treatment, the incidence did not differ between treatment pathways in this study. The increases in IOP that occurred were typically manageable with topical medication. The timing of IOP rises was predictable, and the incidence and magnitude of IOP elevations did not increase upon repeated injection over 12 months probably because patients who were initiated on topical IOP lowering medications continued on the medications until end of the study.

The results of this study suggest that patients need not be reviewed for IOP check at 1 week following Ozurdex injection as no patients developed a rise in IOP at this time-point. In most patients who developed IOP rise, this was observed at the visit 8 weeks post injection. We therefore recommend a post-injection IOP check at about 4-8 weeks especially in eyes with established glaucoma or ocular hypertension or previous history of steroid induced ocular hypertension in both arms.

As previously shown, cataract progression is dose related and more frequent dosing than 6 monthly resulted in a higher proportion of cataract development and progression that affected final visual acuity gain. In the MEAD study, 6 monthly PRN Ozurdex resulted in reduced improvement in BCVA at 15 months from baseline after

a mean of 2.3 injections in the first year. The OZLASE study showed that mandated Ozurdex at baseline and at 16 weeks followed by PRN regimen with a mean of 3.5 injections in 12 months resulted in 21/27 (78%) of eyes showing cataract progression that confounded final visual acuity (personal communication). It should be noted that there is no standard definition of progression of cataract or for the threshold for cataract surgery. Differences in rate of cataract progression reported between studies using varying dosing regimens may not be related to the dosing regimen. We defined cataract progression as a 1-step change in LOC II score while the BEVORDEX study defined as a 2-step change in LOC II grading.

The MEAD study showed that 23.3% of pseudophakic eyes gained 15 or more letters at 3 year follow up compared to 22.2% in the whole study. Our study population also showed that 22% gained 15 or more letters in both arms together with no significant difference in visual outcome in pseudophakic eyes. We believe that intravitreal Ozurdex is very effective in causing resolution of macular fluid. However, unlike the earlier studies such as the MEAD study that included patients with persistent fluid post-laser treatment, recent studies include patients that have been refractory to laser therapy and anti-VEGF agents. Therefore, these are truly refractory cases and visual acuity is unlikely to improve in many of these cases despite complete resolution of macular oedema.

If Ozurdex is planned as an alternate option for patients with refractory DMO, this study suggests that 5-monthly fixed dosing is an effective approach and may be more acceptable to patients. Patients should be warned about cataract progression and that significant gains in visual acuity is less likely compared to anti-VEGF agents.

The strengths of this trial include secure randomisation, size, the multicentre design, low rates of losses to follow-up, and use of outcome measures appropriate to the primary outcome. Limitations of the study include the fact that the 12 month cut off of the study may have been more advantageous to the fixed arm than the PRN arm because all patients received mandated dosing in the fixed arm at 10 months and the maximal effect on vision and macular thickness is expected at 12 months while the injections flexibility in the PRN arm may have meant that not all patients would have attained maximal efficacy by 12 months. However, this did not alter the visual outcome between arms and may only explain the differences in central macular thickness between arms. The non-inferiority margin of 5 letters might be considered large by some and hence a limitation of the study; however, this was selected based on previous studies that showed that a 5 letter change is required for patients to perceive a treatment benefit.[18]The sample size is a limitation of this study. Despite being powered based on equivalent studies, the results showed more variability in the outcome than was anticipated. Recruitment had completed prior to any outcome data being available so adjustment to the sample size during the study was not possible.

To our knowledge, this is the first large prospective, randomized controlled trial of dosing regimens with Ozurdex in DMO. Several studies have compared Ozurdex to other interventions including sham but comparisons between Ozurdex arms in different trials are complicated due to different trial treatment regimen. Owing to the large study population and the strict adherence to accepted research methodology in this trial, the results provide concise data, suggesting that 5-monthly fixed dosing is non-inferior to PRN treatment both in terms of visual outcome and safety profile.

Conclusions

We have provided useful information for clinicians using Ozurdex to treat DMO in patients refractory to laser and or anti-VEGF. Although the visual outcomes are not as effective as those reported with anti-VEGF agents in DMO at one year, if Ozurdex is used, this study suggests that the fixed dosing arm is an alternative treatment regimen for DMO that is as effective as PRN dosing and still has a profound drying effect of the macula.

In summary, this study shows that 5-monthly fixed dosing of Ozurdex is non-inferior to OCT-guided PRN dosing in patients with DMO with a similar safety profile and better feasibility and acceptability. The relative advantages and disadvantages of these treatment regimens should be discussed with DMO patients so that an informed decision can be made.

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15. Appendices List

I. **Ethical Approval**
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I. Ethical approval

NHS
Health Research Authority

NRES Committee London - Harrow
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Tel: 0117 342 1384

06 June 2014

Ms Natasha Ajraam
R&D Moorfields Eye Hospital
162, City Road
London
EC1V 2PD

Dear Ms Ajraam

Study title:	**A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema.**
REC reference:	**12/LO/1534**
Protocol number:	**SS01**
EudraCT number:	**2012-003661-17**
Amendment number:	**Amendment 7**
Amendment date:	**01 May 2014**
IRAS project ID:	**113840**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		29 April 2014
Notice of Substantial Amendment (CTIMP)	Amendment 7	01 May 2014
Other [Response to Committee's Queries]		05 June 2014
Research protocol or project proposal	7	07 March 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

II. MHRA approval

Safeguarding public health

MHRA

Ms N Ajraam
MOORFIELDS EYE HOSPITAL
162 CITY ROAD
LONDON
EC1V 2PD
UNITED KINGDOM

25/10/2012

Dear Ms N Ajraam

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	11412/0219/001-0001
Eudract Number:	2012-003661-17
Product:	OZURDEX
Protocol number:	SS01

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 24/10/2012.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
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An executive agency of the Department of Health

III. Patient information sheet - Version 4.1 dated 07-01-2014

Moorfields Eye Hospital NHS
NHS Foundation Trust

Patient Information Sheet

A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema.

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Contact for queries If you have any questions about this study, you can contact

Research Co-ordinator

Moorfields Eye Hospital

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You are being invited to take part in a research study for a new treatment for diabetic macular oedema (a condition that causes fluid to build up in the central part of the eye's retina affecting eyesight). Before you decide whether to take part, you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is macular oedema?

Damage to the blood vessels in the retina caused by diabetes can cause them to leak fluid which builds up in the macula. The macula is the central part of the retina at the back of the eye. It is responsible for fine vision, such as reading, watching television and recognising faces. The build-up of fluid in the macula damages it and reduces your vision.

What is the purpose of the study?

We are conducting an investigational study of different dosing regimen of Ozurdex for the treatment of diabetic macular oedema. Ozurdex is a long-acting dexamethasone (steroid medicine). This study is designed to assess which regimen affects the macula better.

Why have I been chosen?

You are being asked to take part in this research study because you have refractory macular oedema that is not responding to current standard care. About 100 patients will be taking part. Only one eye will be treated in the trial. The other eye will receive standard care if necessary.

Do I have to take part?

No. Your participation in the study is voluntary. You may choose not to take part in this study or you may leave the study at any time without giving a reason. Your future treatment and care will not be affected.

What will happen to me if I take part?

If you take part, you will be in the study for 12 months. You will be randomised to receive the Ozurdex injections every 5 months if you are in one arm of the study. In the other arm, after the first Ozurdex injection at the start of the study, you will be

reviewed at 4 months and then every month. The next appointment will be in four months time and this cycle will continue until the end of the study. You will need to visit the hospital approximately 6 times during the study period for various tests to assess your eyesight and general health. You will come for a safety check one week and eight weeks after your treatment with Ozurdex. The maximum number treatments with Ozurdex you can receive during the study is three in both study arms.

What types of tests are done?

At your first visit, an ophthalmologist (eye doctor) will do the following tests to see if you are suitable for the study:

1. You will be asked questions about your medical history, your eyesight history and about any medications you are taking.
2. Visual acuity test: this tests how clearly you can see different sized letters on a chart with both eyes.
3. Eye pressure measurement.
4. Blood pressure measurement.
5. Blood test: if you are diabetic we will do a blood test to see what your average blood sugar levels have been over the last three months.
6. Pregnancy test if you are a woman of child-bearing age.
7. Eye Examination: this involves looking closely at your retina for anything unusual and testing the pressure inside each eye. You will be given eye drops before the test to dilate your pupils (make your pupils bigger). You may find bright lights hurt your eyes for 4-6 hours after this test but sunglasses will help. You must not drive until the effects of the eye drops have worn off. This test takes about 5 minutes.
8. Colour photographs will be taken of the retina in each eye. You will be given eye drops before the test to dilate your pupils, as described above. You will notice a bright flash after each photo is taken, but this will not have any long-term effect on your eye. This test takes about 10 minutes.
9. Fluorescein angiography: This test is done very often in clinic. It helps us see what stage your macular oedema is at. The test involves a fluorescent dye being injected in to your hand or arm with a needle. The dye lets us see how much fluid has built up in your macular and we will take photographs of it. You will be given eye drops before the test to dilate your pupils, as described above.

The injection may make you feel faint, may make the vein in your arm/hand swollen or you may have some bruising or bleeding where the injection was done. The fluorescent dye may turn your skin a bit yellow for a few hours. It might also make your urine dark orange for up to 24 hours and you might feel a bit sick. Rarely the dye make leak out of a fragile vein and your skin at the site of the injection might turn yellow for a few days. You might also feel some burning at the site of injection, which usually lasts a few minutes. An allergic reaction to the dye may happen but this is rare. The risk of death from the procedure is less than 1 in 200,000. Generally, this small risk is considered worth it in order to keep your eyesight at its best. This test lasts about 20 minutes.

10. Optical Coherence Tomography (OCT): this test is like an ultrasound for your eye. It lets us take pictures of the back of your eye. You will be given eye drops before the test to dilate your pupils, as described above. The test is quick and painless. For the test, you will sit in front of a machine and a light beam will scan the retina in each eye. This test lasts about 10 minutes.
11. VFQ 25, MacDQoL, RetTSQ: These are three questionnaires that you will need to answer about your vision and quality of life and treatment satisfaction.

What happens next?

If, after the initial tests above, your ophthalmologist decides that you are suitable for the study, you will have your first treatment of Ozurdex.

What types of tests are done at the other visits?

It will be similar to the first visit as detailed above.

1. You will be asked questions about how you have been since your last visit and about any changes to the medications you are taking since you were last seen.
2. Visual acuity to check the vision in both eyes (as above).
3. Eye examination (as above).
4. Optical Coherence Tomography (as above).
5. Colour photographs only at 12 month (as above).
6. Fluorescein angiography only at 12 months . (as above)
7. You will also receive treatment of Ozurdex at any point from the 4th month to the 12th month.

How long should visits take?

It is hard to say but the first visit will be about 4 hours. Other visits will be shorter as there are fewer tests to do – they should take about 2 hours. Only one eye will be chosen as the "study eye", which will be chosen by the study doctor. Only the chosen study eye will receive injections.

What other treatments are there for macula oedema?

Laser photocoagulation – this is the usual treatment that involves placing small laser burns in the area of leakage in the retina. These burns slow the leakage of fluid and reduce the fluid in the eye. This is the only generally accepted treatment. Laser photocoagulation has been shown to improve the vision in only 3% of patients after 3 years. It has been shown that on average laser will stop your vision getting worse. Other medications that act on this condition include ranibizumab (Lucentis) and bevacizumab (Avastin). NICE has approved ranibizumab for a subset of patients with a minimum thickness of macular oedema of 400 µm as measured by an eye-scan. As a result Ranibizumab may be available as standard care at some trusts.

What is the drug being tested?

Ozurdex is the drug being tested. It is designed to reduce the leakiness of the blood vessels in the retina at the back of the eye, and therefore help the symptoms of macular oedema.

What will the Ozurdex injection involve?

Before the injection of Ozurdex, your eye will be prepared with antibiotic and antiseptic eye drops. Then the eyelids will be thoroughly cleaned with a cotton-tip applicator soaked in iodine cleaning solution. The eye is then held open and a local anaesthetic injection is given and anaesthetic eye drops (numbing medication) are dropped onto the lower part of your eye.

After a few minutes Ozurdex will be injected into your vitreous (which is the jelly-like substance inside your eye located between the back of your lens and your retina). Your doctor will give you antibiotic drops to put in your eye for 4 days after the injection.You will be required to attend a safety check 1 week after each injection you have. The maximum number of times you can receive an injection is 2.

Will the injection be very painful?

There will be some amount of pain during the procedure but you will be given an anaesthetic injection and drops (numbing medication) before the procedure to make you more comfortable.

Is the treatment completely safe?

No, the main risk is that your eyesight may get worse despite the treatment. This usually happens because of your macular oedema getting worse, but rarely, it is possible that your vision may get worse as a direct result of the treatment. The risks of Ozurdex are discussed below.

How safe is Ozurdex ?

Ozurdex is available in the NHS and approved by NICE for the treatment of macular oedema caused by retinal vein occlusion (blockages in the veins in the retina). During the follow up visits, you will be checked for potential side effects and the results discussed with you. Any new problems you notice during the study, which may affect your condition or your decision to stay in this study, should be discussed with your study doctor.

Injecting Ozurdex into the eye has risks in itself. The most serious problem which could affect your eye after an injection is infection. This is called endophthalmitis. This occurs because bacteria can enter the eye created by needle hole. To try and stop this happening your eye is treated with antibacterial iodine before the injection. The injection is done in very clean sterile conditions and you are given antibiotic eye drops to take for 4 days afterwards. By this time the eye has healed.

Other known side effects include the formation of cataract or raised intraocular pressure (pressure inside the eye). Our experience from previous trials has indicated that there may be an increased frequency of cataract formation following the use of the Ozurdex. If you do develop cataract, or if your cataract worsens, you may be offered the option of cataract surgery. Your research physician will explain the implications of this and the surgery requirements. You will be required to provide consent for cataract surgery, under the normal hospital consent process. If the pressure in the eye is raised, you may be given eye drops to lower it.

The other rare but serious side effects are retinal detachment (which is when the retina comes away from the back of the eye), bleeding at the back of the eye or damage to the lens from the needle. All together there is about a 1 in 1000 risk of a serious complication with each injection.

What common and less serious side effects are there?

Less serious but more common side effects are a slightly bloodshot eye, temporary visual floaters (small specks like flies flying around in front of your eyes), temporary visual flashes and inflammation of the eye. You may temporarily experience reduced vision after the Ozurdex injection and you must not drive or operate machinery until it is resolved

There may also be a mild temporary increase in the pressure inside the eye (often as a result of the injection). If you have a history of glaucoma, you may be more at risk, so you will only be able to take part in the study if we are sure that your glaucoma is under control.

What should I be aware of and worried about?

It is extremely important that you are aware of any symptoms that might mean you are having one of these problems described above, and that you tell your study doctor immediately about any new symptoms you are having. Any or all of these side effects may cause loss of vision.

The symptoms to be aware of include:

- Eye pain or increased discomfort
- Worsening eye redness
- Blurred or decreased vision
- Increased sensitivity to light
- Increased number of floaters

IF YOUR DOCTOR IS NOT ACCESSIBLE FOR ANY REASON AN ALTERNATE DOCTOR SHOULD BE CONTACTED IMMEDIATELY at the A&E at Moorfields Eye Hospital.

Can I look on the internet for more information?

Yes, you can although you need to be aware of what condition the medication is being used for. The effects of Ozurdex may be different in different causes of macular oedema. Although it may be a good source for general information, it may also be very misleading.

Women only

You must not plan to become pregnant during the study, as we don't yet know whether the study medicine is safe for an unborn baby. A negative pregnancy test within 7 days before starting the first dose of the study drug is required in women who are able to get pregnant, and a repeat pregnancy test must be done if you miss any periods or your menstrual cycle becomes irregular.

Women who are able to have children must not take part in the study unless they are using contraception all the time during the study. Before starting the study, it is strongly recommended that you have been using contraception for at least a month. It is strongly recommended that you do not deliberately become pregnant during this trial. Ideally, you should continue using contraception for 4 weeks after the end of the study. If you become pregnant during the study, you must tell the study doctor immediately and youwill be withdrawn from the study. You will be asked by your research physician to consent to follow your pregnancy until outcome.

Are there any reasons why I should not participate in this study?

You should not participate in this study if you are pregnant or if you are planning to become pregnant or are breastfeeding. You will not be able to participate in any other clinical trial for the whole time you are taking part in this trial. There may be other reasons why you should not take part in this study and these will be explained to you in more detail by The Principal Investigator or one of her team.

How effective may it be?

It is hard to say, and is one of the reasons we are doing this study. Previous studies in patients with the macular oedema due to blocked blood vessels in the retina showed that vision improved after one injection but this effect started to wear off after 6 months. Other on-going studies using this drug for diabetic macular oedema have used either 4 monthly or 5 monthly dosing intervals.

Are there any benefits to me if I participate in this study?

It has been shown that on average the current treatments do not increase vision. It is expected that Ozurdex will increase vision on average by 7 test letters at 6 months, so we believe that your chances of improvement in vision are higher. That is why we want to test the medication and the dosing frequency. However this cannot be guaranteed and it is possible that your condition may get worse.

The information we get from this study may help us develop new treatments for Macula Oedema, which may benefit other patients or yourself in the future.

What if I choose not to take part in the study?

If you do not want to take part in this study, you will receive standard care as decided by your doctor. Your participation in this study is voluntary and you may withdraw from the study at any time without your future medical care being affected. Should you decide to withdraw from the study for any reason, please contact Miss Sivaprasad immediately. You will be informed of any significant information that may develop during the research study that may relate to your willingness to continue in participation as a patient.

Can I withdraw from the trial if I enter it?

If at any time during the study either you or your doctor feels that it is in your best interest to withdraw from this study, you may do so without any penalty or loss of benefits to which you are otherwise entitled to at this hospital, including the present and future standard care. You will be asked to return for a final safety visit. The procedures performed will be the same of those scheduled for final study visit.

What happens when the research study stops?

When the research ends, you will be followed up in our clinics. This drug is likely to become available for routine use but no assurances can be provided at present. If it does not become available, we will follow you up in clinic and provide treatment with the best available standard care which is laser treatment or ranibizumab injections.

Who will know my results?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised people from the hospital sponsoring the research. They may also be looked at by authorised people to check that the study is being carried out correctly. Everyone will have a duty of confidentiality to you as a research participant and we will do our best to meet this. The results of your treatment may be published for scientific purposes; however, your identity will not be revealed.

Will my GP know about the study?

Your GP will be informed that you are participating in the study and kept informed of your medical progress. We may exchange information regarding your general medical health with your GP.

Will the study cost me anything?

You will not be asked to pay for any costs associated with the study protocol or follow-up visits.

Will I receive reimbursement?

You will not receive any monetary compensation for taking part in the study. Your willingness to take part, however, may, in the future, help doctors better understand and/or treat others who have your condition. Subsistence will be provided if any of your visits last more than 4 hours.

What happens if I am harmed in any way?

If any harm occurs while you are taking part in this research project, you will have all the rights and protection that you normally have as an NHS patient. There are no special compensation arrangements for study participants. There is no no-fault legal liability insurance and NHS indemnity is in place. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it.

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints procedures are available to you.

If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Who has reviewed the study?

The study has been approved by Moorfields Eye Hospital Research Governance Committee, the Harrow Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Who is organising and funding the research?

The research is sponsored by Moorfields Eye Hospital NHS Foundation Trust and the research is funded by Allergan Pharmaceutical Company. The doctors conducting the research are not being paid for including and looking after the patients in the study and has no conflicts of interests.

I have some questions, who can I ask?

When you come in on the first visit you can ask the study doctor any questions or you can telephone Miss Sivaprasad's team (contact details are on page 1).

Who do I contact if there is a problem?

If you believe that you are hurt or if you get sick because of something that is done during the study, you should call the research co-ordinator for this study (**020 7 566 2109).** In the event of an emergency after normal working hours you may contact the emergency department at Moorfields Eye Hospital (0207 253 3411). If you have any questions about your rights as a research subject, contact the hospital's PALS department (Patient Advice & Liaison Service). You will be given an opportunity to ask any questions concerning the research and your participation, and Miss Sivaprasad or her colleague will answer your questions. If you choose to participate, you will be given a consent form to sign. By signing the consent form, you have not waived any of your legal rights. You will receive a copy of this consent form that will show all signatures and dates.

Thank you for reading this information and considering taking part in the study.

IV. Consent form - Version 2.1 dated 07-01-2014

Moorfields Eye Hospital NHS
NHS Foundation Trust

City Road
London
EC1V 2PD

Tel: 020 7253 3411
www.moorfields.nhs.uk

Centre: Moorfields Eye Hospital
Name of Researcher: Miss Sobha Sivaprasad
Patient identification Number for this Study:

CONSENT FORM

A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema.

Please initial box

1. I confirm that I have read and understand the information sheet dated 07-01-2014 (Version 4.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or the NHS Trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I understand that my GP will be informed of my participation in this research project and of any findings significant to my general health. ☐

5. I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test. ☐

6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature

_____	_____	_____
Name of person taking consent	Date	Signature

When completed: Original for researcher site file; a copy for the participant; a copy for the medical notes.

V. Trial Personnel

Chief Investigator	Moorfields Eye Hospital Prof. Sobha Sivaprasad	e-mail: sobha.sivaprasad@nhs.net tel: 0207 566 2039. fax: 0207 566 2972
Principal Investigators	Moorfields Eye Hospital Mr Philip Hykin	e-mail: philhykin@aol.com tel: 0207 566 2262. fax: 0207 566 2972
	Wolverhampton & Midland Counties Eye Infirmary Mr Yit Yang	e-mail: yit.yang@nhs.net tel: 01902 307 999 fax: 01902 645 018
	Bristol Eye Hospital Miss Clare Bailey	e-mail: clare.bailey@bristol.ac.uk tel: 0117 342 4653 fax: 0117 928 4653
	Frimley Park Hospital NHS foundation trust Mrs Geeta Menon	e-mail: geeta.menon@fph-tr.nhs.uk tel: 01276526982 fax: 01276522386
	Brighton and Sussex University Hospitals NHS Trust Mr Michael Eckstein	Tel: 01273 606126 fax: 01273 693674
Medical Statistician	Moorfields Eye Hospital Catey Bunce	e-mail: Catey.bunce@moorfields.nhs.uk tel: 020 7566 2820 fax: 020 7566 2019
Randomisation Services	Clinical Trials Unit, King's College London Caroline Murphy	email: caroline.murphy@kcl.ac.uk tel: 020 7848 0532 fax: 020 7848 5229
Web based database	Clinical Trials Unit, King's College London Joanna Kelly	email: Joanna.kelly@kcl.ac.uk tel: 020 7848 0532 fax: 020 7848 5229
Pharmacy	Moorfields Eye Hospital Rachael Yoon	e-mail: Racheal.yoon@moorfields.nhs.uk tel/fax: 0207 566 2360
Trial Monitoring	G Lambert Consulting Ltd Gill Lambert	Email: gill@wendyfisherconsulting.co.uk Tel 07727 818 476

Trial Steering Committee	Western Eye Hospital Dr Sheena George (Chair)	Tel 02033127724 Fax: 07930550860
	Sobha Sivaprasad	
	Phil Hykin	
	Catey Bunce	
	Geeta Menon	
Data Monitoring Committee	Essex County Hospital Mr Jignesh Patel (Chair)	Email: jigs37@hotmail.com Tel. 01206 744611
	Queen's Hospital, Mr Niaz Islam	Email: isniaz@yahoo.com Tel: 07931708440
	Cheltenham General Hospital Dr Irene Stratton	irene.stratton@nhs.net

VI. Curriculum vitae

CURRICULUM VITAE	
Sobha Sivaprasad	**Consultant Ophthalmologist (Medical Retina)** **Moorfields Eye Hospital and King's College Hospital**

Qualifications

DM	Cranfield University	2005
FRCSEd	Royal College of Edinburgh	1997
DNB	National Board, New Delhi	1991
M.S Ophth	University of Kerala, India	1990
D.O	Mahatma Gandhi University, India	1988
MBBS	University of Kerala, India	1986

Previous appointments in the last 5 years

Consultant Ophthalmologist, Mid Yorkshire NHS Trust, Wakefield	April 2007 to May 2008
Medical Retina Fellow, Moorfields Eye Hospital, London	Jan 2005 to March 2007
Clinical Research Fellow, King's College Hospital	May 2003-December 2005

Affiliations to Professional Bodies

Fellow of the Royal College Edinburgh
Member of the Royal College of Ophthalmologists
Member of American Society of Retinal Surgeons
Member of American Academy of Ophthalmology
Member of Association for Research in Vision and Ophthalmology
Member of European Vision and Eye Research
Moorfields Eye Hospital Alumni Association

Editorial responsibilities:

Section Editor: EYE
Section Editor: Clinical Ophthalmology
Reviewer for: Ophthalmology, IOVS, Archives, AJO, Current Eye Research, Retina, BJO, Acta, Drugs and Aging.
Grant reviewer: Wellcome, Fight for Sight, Diabetes UK, HTA

National level engagements

Represented RCOphth for NICE scoping meeting for retinal vein occlusion
Represented RCOphth for NICE scoping meeting for Macugen for diabetic macular oedema
Peer reviewer for National Screening Committee for screening of diabetic retinopathy

BME subcommittee member of RNIB

Section Editor – EYE journal

RCOphth writing committee for RVO guidelines

RCOphth – AMD subcommittee member

Other Professional Activities (current)

Research lead for Ophthalmololgy, KCH

Peer reviewer, National Screening Committee for Diabetic Retinopathy

Current Grants:

Guide Dogs for the Blind:

The study of prevalence of visual impairment in diabetic retinopathy in the UK (DRIVE UK study)

Value of grant: £118,000 (PI) –completed April 2012

KCH Research Initiative Grant: SEL-DRS study: Risk factors of diabetic retinopathy.

Value of grant: £98,000 (PI) - Completed November 2012

Moulton Charity Trust

Laser prophylaxis for age related macular degeneration

Value of grant: £250,000 (PI) (initiation April 2011)

Income obtained from **commercial grants**: £370,000

Supervisor for MD/PHD/undergraduate students

1. Completed Clinical supervisor of 1 DM student Cranfield University 2011
2. Clinical supervisor of 2 doctors for DM students Cranfield University.
3. Clinical supervisor of 1 PHD (KCL) Completed 2012
4. Supervisor of 4 SSM undergraduate (3 clinical projects and 1 library projects) completed

Collaborations

City University – CAD system with Prof John Barbur

City University –Prof Geoff Arden

Diabetes Research Centre – Guy's Hospital – Afhsan Malik - NSA mRNA and Mitochondrial DNA analysis in diabetic retinopathy

MicroRNA in diabetic retinopathy – collaborator Prof Manuel Mayr, Cardiovascular Division, KCL

Selected peer-reviewed publications (in chronological order in the last year): 78 publications

1: Sivaprasad S, Gupta B, Gulliford MC et al.Ethnic Variations in the Prevalence of Diabetic Retinopathy in People with Diabetes Attending Screening in the United Kingdom (DRIVE UK). PLoS One. 2012;7(3):e32182.

2: Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. Expert Rev Med Devices. 2012 Mar;9(2):189-97.

3: Sivaprasad S, Bunce C, Crosby-Nwaobi R. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Cochrane Database Syst Rev. 2012 Feb 15;2:CD004239.

4: Arden GB, Sivaprasad S. The pathogenesis of early retinal changes of diabetic retinopathy. Doc Ophthalmol. 2012 Feb 3. [Epub ahead of print]

5: Gupta B, Wong R, Sivaprasad S, Williamson TH. Surgical and visual outcome following 20-gauge vitrectomy in proliferative diabetic retinopathy over a 10-year period, evidence for change in practice. Eye (Lond). 2012 Jan 13. doi: 10.1038/eye.2011.348. [Epub ahead of print] PubMed PMID: 22241020.

5: Shona O, Gupta B, Vemala R, Sivaprasad S. Visual acuity outcomes in ranibizumab-treated neovascular age-related macular degeneration; stratified by baseline vision. Clin Experiment Ophthalmol. 2011 Jan; 39(1):5-8.

6: O'Neill-Biba M, Sivaprasad S, Rodriguez-Carmona M, Wolf JE, Barbur JL. Loss of chromatic sensitivity in AMD and diabetes: a comparative study. Ophthalmic Physiol Opt. 2010 Sep; 30(5):705-16.
7: Sivaprasad S, Elagouz M, McHugh D, Shona O, Dorin G. Micropulsed diode laser therapy: evolution and clinical applications. Surv Ophthalmol. 2010 Nov-Dec; 55(6):516-30. Epub 2010 Sep 20.
8: Vemala R, Gupta B, Sivaprasad S. Visual outcome of ranibizumab therapy for neovascular age related macular degeneration in the black population: a report of five cases. Clin Ophthalmol. 2010 Aug 19; 4:913-6.
9: Gupta B, Adewoyin T, Patel SK, Sivaprasad S. Comparison of two intravitreal ranibizumab treatment schedules for neovascular age-related macular degeneration. Br J Ophthalmol. 2011 Mar; 95(3):386-390. Epub 2010 Aug 6.
10: Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, Dowler J, Majid MA, Bailey C, Mohamed Q, Johnston R, Bunce C, Xing W; ABC Trial Investigators. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ. 2010 Jun 9; 340
11: Gulliford MC, Dodhia H, Chamley M, McCormick K, Mohamed M, Naithani S, Sivaprasad S. Socio-economic and ethnic inequalities in diabetes retinal screening. Diabet Med. 2010 Mar; 27(3):282-8.
12: Gulliford MC, Dodhia H, Sivaprasad S, Ashworth M. Family practices' achievement of diabetes quality of care targets and risk of screen-detected diabetic retinopathy. PLoS One. 2010 Apr 29; 5(4):e10424.
13: Elagouz M, Jyothi S, Gupta B, Sivaprasad S. Sickle cell disease and the eye: old and new concepts. Surv Ophthalmol. 2010 Jul 8; 55(4):359-77.
14: Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010 Jun; 117(6):1134-1146.e3.
15: Gupta B, Jyothi S, Sivaprasad S. Current treatment options for retinal angiomatous proliferans (RAP). Br J Ophthalmol. 2010 Jun; 94(6):672-7. Epub 2009
16: Jyothi S, Chowdhury HR, Chong V, Sivaprasad S. Anti-VEGF therapy for choroidal neovascularisation previously treated with photodynamic therapy. Eye (Lond). 2010 Jun; 24(6):1018-23.
18: Sivaprasad S, Hykin P, Saeed A, Beatty S, Grisanti S, Staurenghi G, Olea JL, Campos A, Barbosa A, Rito L, Silva R, Faria R, Eldem B, Kadayifçilar S, Kolar P, Feucht N, Maestroni L. Intravitreal pegaptanib sodium for choroidal neovascularisation secondary to age-related macular degeneration: Pan-European experience. Eye (Lond). 2010 May; 24(5):793-8.
19: Jyothi S, Chowdhury H, Elagouz M, Sivaprasad S. Intravitreal bevacizumab (Avastin) for age-related macular degeneration: a critical analysis of literature. Eye (Lond). 2010 May; 24(5):816-24.
20: Gupta B, Elagouz M, Sivaprasad S. Intravitreal bevacizumab for choroidal neovascularisation secondary to causes other than age-related macular degeneration. Eye (Lond). 2010 Feb; 24(2):203-13.
21: Salam A, DaCosta J, Sivaprasad S. Anti-vascular endothelial growth factor agents for diabetic maculopathy. Br J Ophthalmol. 2010 Jul; 94(7):821-6.

Lectures and presentations 2012

27 presentations in national meetings, 4 presentations in international meetings,

Prepared ‘laser’ module for RCOphth elearning.

Prepared the RAP chapter for Ophthalmolopedia.

Book Chapters

1. **Sivaprasad S**, Okhravi N, Lightman S: Sarcoidosis in the Text Book ‘**Retinal Vascular Disease’** by Antonia Joussen, Thomas Gardner, Bernd Kirchhof and Steven Ryan. Springer publications 2007 **ISBN**-10: 3540295410

2. **Sivaprasad S**, Hykin P: Toxic Retinopathies in the Text Book ‘**Ophthalmology Secrets’** by James F. Vander, Janice A. Gault: Hanley & Belfus publications 2007. **ISBN-10:** 0-323-03469-1

3. Victor Chong, MD, Ricardo Luiz Smith, MD, PhD, and Sobha **Sivaprasad**, MD Retinal biochemistry, physiology and cell biology in **Retinal Pharmacotherapy**. Elsevier publications 2009 **ISBN 10:** 1-4377-0603-7
4. Sobha **Sivaprasad,** Raeba Mathew Diabetic Eye Disease in **Diabetes and its management**. Wiley Publishers 2011 **ISBN**: **1405107251**

VII. Study protocol - OZDRY Protocol SS01 Version 7.0. dated 07-03-2014

Moorfields Eye Hospital NHS Foundation Trust

Full title of trial	**A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema.**
Short title	OZDRY
Version and date of protocol	Protocol SS01 Version 7.0 dated 07-03-2014
Sponsor:	Moorfields Eye Hospital NHS Foundation Trust
Funder (s) :	Allergan Pharmaceuticals
Clinical trials.gov	NCT01892163
EudraCT no	2012-003661-17
ACTIVE IMP(s):	700µg dexamethasone posterior segment drug delivery system (DEX PS DDS)
PLACEBO IMP(s):	NA
Trial sites(s)	Multicentre
Chief investigator: Miss Sobha Sivaprasad Moorfields Eye Hospital 162, City Road, London EC1V 2PD	**Sponsor Representative**: Maria Hassard, Deputy Director R&D Moorfields Eye Hospital NHS Foundation Trust 162, City Road, London, EC1V 2PD Tel 0207 566 2036 Fax 0207 566 2315

Signatures

The Chief Investigator and the RMC have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol except in case of medical emergency) or where departures from it are mutually agreed in writing.

The investigator agrees to conduct the trial in compliance with the protocol, GCP and UK Regulations for CTIMPs, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005), the Sponsor's SOPs, and other regulatory requirements as appropriate.

Chief investigator

Sobha Sivaprasad

Moorfields Eye Hospital Signature Date

Sponsor Representative

Maria Hassard,
Deputy Director R&D
Moorfields Eye Hospital

Signature Date

Contents

List of abbreviations

ADA	American Diabetes Association
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Adverse Reaction
BCVA	Best Corrected visual acuity
BRVO	Branch Retinal Vein Occlusion
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CRVO	Central Retinal Vein Occlusion
CST	Central sub-field thickness
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
DEX PS DDS	Dexamethasone Posterior Segment Delivery system
DMC	Data Monitoring Committee
DMO	Diabetic macular oedema
DR	Diabetic Retinopathy
DSUR	Developmental Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FAZ	Foveal Avascular Zone
FFA	Fundus Fluorescein Angiography
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practioner
HbA1C	Glycosylated Haemoglobin
IB	Investigator Brochure

ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Random Clinical Trials Number
MA	Marketing Authorisation
MEH	Moorfields Eye Hospital
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence
NIMP	Non-investigational medicinal product
OCT	Optical Coherence Tomography
OD	Oculus Dexter, right eye
OS	Oculus Sinister, left eye
OU	ocular uterque, both eyes
PDR	Proliferative diabetic retinopathy
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Per Protocol
PRN	Pro re nata
PRP	Pan retinal photocoagulation
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
RetDQOL	Diabetic retinopathy quality of life
Ret TSQ	Treatment Satisfaction Questionnaire
RMC	Research Management Committee
RVO	Retinal Vein Occlusion
SAR	Serious Adverse Reaction

SAE	Serious Adverse Event
SE	Study Eye
SDV	Source Document Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VFQ 25	Visual function questionnaire
WHO	World Health Organisation

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Summary

Title:	**A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema (DMO).**
Short title:	OZDRY
Trial medication:	700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS).
Objectives:	Primary objective: To evaluate whether 5 monthly fixed dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) is as efficacious as OCT-guided PRN dosing in terms of mean change in best corrected visual acuity in patients with refractory DMO. Secondary objectives: 1. To evaluate the effects of fixed dosing relative to PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) on patient reported outcomes in patients with refractory DMO 2. To evaluate the safety of fixed dosing relative to PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory DMO. 3. To evaluate the effects of fixed dosing relative to PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) on anatomical changes in patients with refractory DMO
Type of trial:	A multicentre, prospective, parallel assigned, open-labelled study comparing the efficacy of two treatment regimens of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory DMO
Trial design and methods:	This is a multicentre study to assess the efficacy of 5 monthly fixed dosing versus OCT-guided PRN dosing of intravitreal 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory DMO

	defined as central sub-field thickness (CST) exceeding 300µm despite laser and/or antiVEGF treatments. After informed consent, patients will undergo baseline examinations of best corrected visual acuity (BCVA), optical coherence tomography (OCT), autofluorescence, and 4 field retina colour photos and fundus fluorescein angiography (FFA) and complete questionnaires on quality of life and treatment satisfaction. Patients will be randomised 1:1. Fixed dosing arm will have mandatory doses of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) at baseline and thereafter every 5 months unless criteria for deferred treatment is met. Participants in the OCT-guided PRN dosing arm will be treated at baseline and then at any visit thereafter if CST is more than 300 µm but the interval between consecutive injections should not be less than 16 weeks. The final follow-up will be at month 12. Efficacy measures include BCVA in ETDRS letters; central retinal thickness (CRT) and number of treatments. Patient reported outcomes will be recorded using visual function questionnaire VFQ25, RetDQoL and treatment response questionnaire using RetTSQ. Safety measures include increased IOP, cataract surgery and other adverse events
Trial duration per participant:	12 months
Estimated total trial duration:	30 months
Planned trial sites:	Multicentre – 5 sites.
Total number of participants planned:	100 patients
Main inclusion criteria:	Patients with diabetes of either gender, aged 18 or above having visual impairment due to refractory centre-involving diabetic macular oedema despite macular laser and/or antiVEGF treatment. Best corrected visual acuity in the study eye must be between ≥ 34 and ≤ 73 ETDRS letters. The central sub-field thickness should be >300µm on Spectralis

	OCT.
Statistical methodology and analysis:	ITT: Analyses will be by intention to treat to retain the validity of the randomisation process and all participants randomised will be included. PP: This will include all randomised and treated participants without major protocol deviations which will be defined prior to database lock. Safety population includes all participants who received the study medication. Significance levels of tests: The primary outcome will be tested using a 1-sided p-value, and presented with a 1-sided 95% confidence interval (or equivalently a 2-sided 90% confidence interval). All other statistical tests will use a 2-sided p-value of 0.05 and be presented with a 2-sided 95% confidence interval, unless otherwise specified. Primary efficacy: The null hypothesis is that the difference in BCVA at 12 months between the two arms is >5 letters. The alternate hypothesis is that the BCVA at 12 months in the fixed dosing arm is no more than 5 letters less than the OCT-guided PRN dosing arm. A 1-sided 95% confidence interval (or equivalently a 2-sided 90% confidence interval) will be estimated using an analysis of variance (ANOVA) model with treatment group as the main effect. Baseline comparability: Baseline characteristics will be summarised by randomised group to determine if the treatment groups are comparable. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Covariates such as HbA1C, baseline retinal thickness and previous number of treatments and others deemed appropriate will be included in the analyses.

Introduction

Background

Diabetic retinopathy (DR) is the most prevalent microvascular complication in people with diabetes. Visual loss from diabetes results primarily from two ocular complications. DR can progress to a stage called proliferative diabetic retinopathy (PDR), where new vessels proliferate on the retina. PDR accounts for the majority of severe visual loss and is generally treated with laser panretinal photocoagulation (PRP). In addition, retinal vessels can become permeable and cause swelling of the centre of the retina, called diabetic macular oedema (DMO). Centre-involving DMO is a leading cause of moderate visual loss in diabetes. To date, the only proven modalities that reduce the risk of visual loss from DMO are intensive glycaemic control, as demonstrated by the Diabetes Control and Complications Trial (DCCT) for Type I diabetics, the United Kingdom Prospective Diabetes Study (UKPDS) for Type II diabetics, blood pressure control as demonstrated by the UKPDS and conventional macular laser therapy. Macular laser photocoagulation was analysed in the Early Treatment of Diabetic Retinopathy Study (ETDRS) and remains the mainstay of treatment.
Macular laser reduces the risk of moderate visual loss by approximately 50% (from 24% to 12%) at 3 years after initiation of treatment in patients with DMO without central ischaemia. Thus the principal aim of macular laser photocoagulation is to prevent visual loss, rather than to improve vision and this was effective in 50% of cases. Visual acuity improved in only 3% (15 letter gain at 3 years) of all study participants although visual acuity was 6/12 or better

in the majority at baseline making improvement unlikely. The treatment can be repeated a number of times but despite this and optimal blood sugar and hypertensive control, there are still many cases in which chronic macular oedema refractory to laser treatment persists.
This has led investigators to consider alternative treatment options for DMO. More recently, investigators have considered the use of anti-VEGF agents e.g. pegaptanib sodium, ranibizumab and bevacizumab in DMO. A small two year prospective randomised trial (BOLT study) of modified ETDRS macular laser therapy versus. repeated injections with the pan anti-VEGF agent, bevacizumab reported results at 24 months and showed a +8.5 letter difference in best corrected visual acuity between the two groups in favour of bevacizumab. The visual outcomes with bevacizumab in the BOLT study are in line with several recent ranibizumab for DMO treatment studies. In the 12 month RESOLVE study, visual acuity (mean ± SD) improved by 10.3 ± 9.1 letters compared to baseline

with ranibizumab and declined by 1.4 ± 14.2 letters with sham. The RESTORE study showed that at 1 year, 37% of subjects treated with ranibizumab alone and 43% of those treated with ranibizumab + laser therapy had a significant improvement in visual acuity of 10 letters, compared to 16% of subjects treated with laser alone. The mean increase in letter score was ranibizumab only 6.8, ranibizumab + laser 6.4, laser alone 0.9. In a DRCR.net study, two ranibizumab study arms received three mandated injections followed by as required dosing according to a predefined algorithm, based on visual acuity, clinical findings and OCT outcome. Subjects received a median of 8 injections in the ranibizumab + prompt laser and 9 in the ranibizumab + deferred laser groups in year 1 with 2 and 3 injections respectively in year 2. The study found at 2 years, mean change in visual acuity from baseline was significantly greater in the ranibizumab + prompt laser (mean +5.0 letters, $p<0.01$) and ranibizumab + deferred laser (mean + 7.2, $p<0.001$) than in the sham + prompt laser arm.

Taken together these studies suggest PRN pan-anti-VEGF therapy achieves a 1 to 1.5 line gain in VA at 2 years versus laser therapy, with 50% of subjects achieving a 2 line gain in VA with no definite safety difference between the two. However, 50% of individuals with DMO are refractory to anti-VEGF treatment or require multiple and frequent injections to maintain their vision. The BOLT study was done on patients with persistent oedema following laser treatment and it concluded that a median of 9 and 4 bevacizumab injections were required in the 1st and 2nd year to maintain vision. So it highlights that refractory DMO remains a significant unmet need in this population group. An ideal alternative agent should show similar improvement in visual acuity but last longer and have better or equivalent safety profile than the current antiVEGF agents. This agent should also require less frequent monitoring and less number of injections to reduce the current burden on resources with antiVEGF agents.

Steroids

Steroids inhibit the production of prostaglandins at a higher level in the biochemical pathway, by inhibiting the enzyme phospholipase A2, which catalyses the conversion of membrane lipids to arachidonic acid. By this process, steroids inhibit the formation of both prostaglandins and leukotrienes. Locally their vasoconstrictive properties decrease intracellular and extracellular oedema, suppress macrophage activity, and decrease lymphokine production. Corticosteroids may be administered topically, by periocular injection, orally and parenterally. Topical corticosteroids penetrate the corneal epithelium and reach the anterior chamber. Intravitreal injection of triamcinolone acetonide has become a popular treatment, subsequently, a number of corticosteroid-based intravitreal

implants have been developed to provide a sustained release of drug and make repeated intravitreal injections unnecessary. A promising treatment modality for subjects poorly controlled or intolerant to repeated periocular corticosteroid injections, systemic corticosteroids, or steroid sparing immunosupressive agents has been suggested with the introduction of intraocular steroid-sustained drug delivery devices. It has been shown that these devices are nontoxic and produce constant intraocular drug levels for an extended period in human and experimental models. There are currently four corticosteroid-based intravitreal implants under development. These include the dexamethasone biodegradable implant (Ozurdex®, Allergan, Irvine, CA), the helical triamcinolone acetonide implant (I-vation™ TA, SurModics, Eden Prairie, MN), the fluocinolone acetonide implant (Retisert®, Bausch and Lomb, Rochester, NY), and the fluocinolone acetonide – based implant that is injectable (Medidur™, pSivida, Boston, MA/Iluvien Alimera Sciences, Alpharetta, GA). Triamcinolone acetonide has been reported to be effective in the management of macular oedema because it suppresses inflammation, reduces extravasation of fluid from leaking blood vessels, inhibits fibrovascular proliferation, and downregulates production of VEGF. Triamcinolone can be administered by several routes, including intravitreal depot injection, periocular injection, posterior subtenon injection, and intravitreal implant. After depot injection, corticosteroid action peaks at 1 week, with residual activity persisting for 3 to 6 months. Intravitreal injection of triamcinolone is associated with significant adverse events, including elevated intraocular pressure in up to half of injected eyes and cataract formation, as well as injection-related complications such as endophthalmitis.

Investigational medicinal product

Ozurdex treatment (as per SPC 28/05/2013)

The Ozurdex (Allergan Inc.) drug delivery system is a sustained-release formulation for posterior-segment delivery of dexamethasone, made of a polylacticglycolic acid (PLGA) matrix. It received its marketing authorisation (EU/1/10/638/001) on 27th July 2010 as Ozurdex 700 micrograms intravitreal implant in applicator for macular oedema secondary to retinal vein occlusions. It has subsequently been approved by NICE for treatment of retinal vein occlusion within the NHS in England and Wales.

The recommended dose is one Ozurdex implant to be administered intra-vitreally to the affected eye. Repeat doses should be considered when a subject experiences a response to treatment followed subsequently by a loss in visual

acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. No dose adjustment is required for elderly subjects.
1 pack contains 1 sustained release sterile implantable rod shaped implant containing 700 micrograms of dexamethasone, located in the needle (stainless steel) of a disposable applicator. The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab. The applicator containing the implant is packaged in a sealed foil pouch containing desiccant.

Preclinical data

In a 6-month monkey study following a single intravitreal injection of Ozurdex the dexamethasone vitreous humour C_{max} was 100 ng/ml at day 42 post-injection and 5.57 ng/ml at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection. The rank order of dexamethasone concentration was retina> iris> ciliary body> vitreous humour> aqueous humour> plasma.
In an *in vitro* metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed. This is consistent with results from rabbit and monkey ocular metabolism studies (30). Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine. The Ozurdex matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water. No mutagenicity, carcinogenicity, reproductive or developmental toxicity data are available for Ozurdex. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application. Dexamethasone exposure to the healthy/untreated eye via contralateral diffusion has been observed in rabbits following delivery of the implant to the posterior segment of the eye.

Clinical data

The clinical safety of Ozurdex has been assessed in two Phase III randomised, double-masked, sham-controlled studies in subjects with macular oedema following central retinal vein occlusion or branch retinal vein occlusion (29). A total of 427 subjects were randomised to Ozurdex and 426 to sham in the two Phase III studies. A total of 401 subjects (94 %) randomised and treated with Ozurdex completed the initial treatment period (up to day 180). A total of 47.3 % of subjects experienced at least one adverse reaction. The most frequently reported adverse reactions in subjects who received Ozurdex were increased intraocular pressure (24.0 %) and conjunctival haemorrhage (14.7 %). The adverse reaction profile for

BRVO subjects was similar to that observed for CRVO subjects although the overall incidence adverse reactions was higher for the subgroup of subjects with CRVO. The following adverse reactions, considered related to Ozurdex treatment were reported during the two Phase III clinical trials:

Increased intraocular pressure (IOP) with Ozurdex peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. During the initial treatment period, 0.7 % (3/421) of the subjects who received Ozurdex required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2 % (1/423) with sham.

The adverse reaction profile of 341 subjects analysed following a second injection of Ozurdex, was similar to that following the first injection. A total of 54 % of subjects experienced at least one adverse reaction. The incidence of increased IOP (24.9 %) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180.

Ozurdex in DMO

The phase 2 trials involving eyes with persistent macular oedema showed 35 percent of eyes receiving 700 micrograms improved 10 letters or more by Day 90, compared with 24 percent of those receiving 350 micrograms, and 13 percent in the observation group trial. The trial also showed that Ozurdex reduced central retinal thickness and fluorescein leakage (90 days after treatment). The phase 2 study enrolled 315 patients; of these, 57 in the observation group and 57 in the 700-µg dexamethasone DDS group had DMO. At baseline, most patients were described as having 2 or more patterns of DMO. The number of patients with each pattern was similar between the 2 study groups (focal DMO: observation, 49; dexamethasone DDS, 47; cystoids oedema: observation, 33; dexamethasone DDS, 33; diffuse oedema: observation, 46; dexamethasone DDS, 48; cystoid-diffuse: observation, 25; dexamethasone DDS, 26). There were no significant differences in mean age, baseline BCVA, baseline retinal thickness, or racial or sex distributions between patients with different patterns of DMO. At day 90 among all patients with DMO, a significantly greater proportion of patients in the 700-µg dexamethasone DDS group had achieved improvement of 10 or more letters from baseline BCVA (19 of 57 patients [33.3%]) than did patients in the observation group (7 of 57 patients [12.3%]) (*P*=.007). This significant difference was maintained within the different DMO pattern categories..

The improvements in retinal thickness mirrored those seen for BCVA. Among all patients with DMO, the mean decrease in retinal thickness at day 90 was significantly greater in the 700-µg dexamethasone DDS group (mean decrease, 132.2 µm) than in the observation group.

Another trial that compared Ozurdex and laser therapy versus laser therapy (PLACID) in 232 subjects showed that when Ozurdex is given at baseline and optionally at month 6 and 9, the proportion of subjects with a 10 letter gain at all time points up to 12 months was statistically significantly better than laser treatment only. However, the study also showed that to obtain a sustained effect of Ozurdex, the treatment should be repeated earlier based on macular thickness on OCT and visual acuity.

Another Phase 2 trial recruited 171 patients with persistent macular oedema of more than or equal to 90 days duration to evaluate the safety and efficacy of a dexamethasone intravitreous DDS in eyes with DMO. Patients were randomized to treatment with 700 µg or 350 µg of dexamethasone DDS or observation. At day 90, a BCVA improvement of 10 letters or more was seen in more eyes in the 700-µg group (33.3%) and 350-µg group (21.1%) than the observation group (12.3%; P=.007 vs 700-µg group). At day 180, a BCVA improvement of 10 letters or more was seen in 30% of eyes in the 700µg group, 19% in the 350-µg group, and 23% in the observation group. There were also significantly greater improvements in central retinal thickness and fluorescein leakage in treated eyes than observed eyes (P=.03; day 90). Dexamethasone DDS was well tolerated. The authors concluded that treatment with 700 µg of intravitreal dexamethasone DDS is well tolerated and produces significant improvements in BCVA, central retinal thickness, and fluorescein leakage compared with observation (statistically significant at day 90).

There are ongoing clinical trials examining Ozurdex for the treatment of DMO. Allergan is conducting the Phase 3study on 510 patients comparing Ozurdex 6 monthly with sham and the study is due to be completed in June 2013. Allergan is also comparing 5 monthly Ozurdex versus ranibizumab monthly monitoring and treatment on 300 patients with DMO. The OZLASE study is comparing the visual outcomes of Ozurdex with laser versus macular laser in 80 patients with early DMO with visual acuity better than 54 letters. The dosing regimen is mandatory dosing at 0 and 18 weeks and then PRN based on re-treatment criteria. The OCTOME study is correlating the structure and function of 32 patients with chronic macular oedema treated with Ozurdex over 36 weeks.

Rationale and risks/benefits

There are 240,000 patients with sight threatening DMO in the UK and 48,000 new patients are diagnosed with this condition every year. The standard of care for these patients is laser treatment. Only 50% respond to repeated laser treatment. The laser non-responders are often left untreated or treated with intravitreal triamcinolone or antiVEGF agents. Repeated antiVEGF injections are required for these patients and

only 50% of these patients respond at 2 years. So there is a substantial need for a treatment for refractory macular oedema in approximately 60,000 existing patients with no treatment options and a further 60,000 on repeated intravitreal antiVEGF agents just to maintain their vision. So, a drug delivery system that can be administered with the ability to provide a sustained release of the steroid is useful in these conditions. Pharmacokinetic studies show that Ozurdex provides sustained release of dexamethasone for up to 6 months and therefore may be ideal for the early management of DMO. Secondly, steroid (triamcinolone) is associated with side effects such as cataract and glaucoma while studies on Ozurdex have a far superior safety profile. Lastly, this trial is justified on the basis that there is good evidence to date of the efficacy of intravitreal Ozurdex with a maximum of +10 letter gain in eyes with macular oedema secondary to retinal vein occlusions (GENEVA trial) and uveitis (HURON trial). It is expected that Ozurdex will have similar results in DMO.

Rationale for dosing regimen of Ozurdex

Fixed dosing: The intervention arm of 5-monthly dosing regimen follows extensive review of the data generated from the two Allergan pivotal phase III studies (GENEVA) [Allergan data on file]. In the GENEVA studies treatment (DEX DDS 700µg or Ozurdex or sham) was administered at baseline and then further treatment (Ozurdex) was given at the day 180 visit (unless the patient had a visual acuity of > 84 letters and an OCT <250microns) being the start of an open label follow up period. Analysis of the data revealed approximately half the study population returned for their day 180 visit early (day 136-179) and the remaining study population returned late (day 181-210). The data for all patients treated with Ozurdex returning up to and including day 180 show that patients were performing better in terms of visual acuity gain (> 15 letters gained) than those returning late (26.4% v 16.9%). Thus in order to maximise efficacy as measured by visual acuity, patients should be retreated in the 136-180 day period [Allergan data on file]. So Allergan now recommends 5 monthly dosing in clinical care and in on-going clinical studies. The 024 Allergan study comparing Ranibizumab and Ozurdex has Ozurdex on 5 monthly fixed dosing based on this analyses of the GENEVA study data. The company assumes that this regimen will ensure optimal risk-benefit ratio.

PRN dosing: The approved European SPC for Ozurdex indicates that repeat treatments should be considered when a patient experiences a response to treatment followed by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. Furthermore, patients who experience and retain improved vision or who experience deterioration in vision which is not slowed by Ozurdex should not be retreated. This means that all patients will be followed up monthly after 4 months to assess the need for re-treatment incurring a lot of hospital visits. However, this approach allows a patient centred and individualised

approach and will ensure optimal outcome for each patient. Currently there is no data that suggest that this regimen is as good to the 5 monthly dosing proposed by the company and there is a gap in the scientific knowledge on best dosing regimen for Ozurdex in this patient population. This study will compare the effects of fixed dosing versus PRN dosing of Ozurdex in patients with refractory DMO. So this study will provide new knowledge on the best dosing schedule that would provide optimal visual benefit with minimal burden on patients and hospital services.

Assessment and management of risk

Ozurdex is already NICE approved for macular oedema due to retinal vein occlusions since 2011. All the trial centres in this study have established Ozurdex services. No new safety concerns have been raised except those mentioned in the SPC. There are several on-going Phase 3 trials of Ozurdex in DMO. Intravitreal delivery of study drug has been in routine use in Medical Retina Clinics in UK since 2005. Moorfields Eye Hospital NHS Trust has sponsored several studies that use investigational medicinal products delivered by intravitreal route including Ozurdex. All the trial centres have participated in various CTIMPs for macular oedema.

All AE and SAE will be reported at any point in the study. Standard AE and SAE templates will be used. All AEs will be reported to the appropriate medical team. All SUSARs will be recorded on a SUSAR form and immediately reported to the RMC and forwarded to the MHRA within the specified timeframe. All AEs and SAEs will be discussed at the DMC. The DMC will review the accruing trial data and on-going safety issues. If there are any issues that need further action, these will be escalated to the Trial Steering Committee who will then decide whether the study continues, terminates or if any substantial changes to the protocol are required.

Objectives

Primary objective: To evaluate whether 5 monthly fixed dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) is as efficacious as OCT-guided PRN dosing in terms of mean change in visual acuity in patients with refractory DMO.

Secondary objectives:

1. To evaluate the effects of fixed dosing relative to PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) on patient reported outcomes in patients with refractory DMO

2. To evaluate the safety of fixed dosing relative to PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory DMO.

3. To evaluate the effects of fixed dosing relative to PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) on anatomical changes in patients with refractory DMO

Trial design

Overall design

This is a multicentre, open-label, randomized 12-month study aimed to compare the efficacy of 5 monthly fixed dosing versus OCT-guided PRN dosing of intravitreal Ozurdex in patients with refractory DMO with central sub-field thickness (CST) exceeding 300µm despite 1 laser and/or antiVEGF treatment.

Consenting patients will undergo baseline examinations of best corrected visual acuity (BCVA), optical coherence tomography (OCT), macular stereo and 4 field retina colour photos and fundus fluorescein angiography (FFA) to evaluate patient eligibility. If eligible, the participant will be randomized in a 1:1 ratio to be in one of the treatment arms of the study.

Summary of Treatment and dosing being compared

In the intervention arm (fixed dosing), mandated dose of intravitreal Ozurdex is given at baseline, 5 and 10 months if the criteria for deferred treatment are not met at those time-points.

In the standard arm (PRN dosing) re-treatment with Ozurdex is given after the baseline injection if retreatment criteria are met provided the interval between two consecutive injections should exceed 16 weeks. Re-treatment with Ozurdex is indicated in this arm if the following criteria are met:

Re-treatment criteria

1. CST exceeds 300 µm AND
2. i) IOP ≤ 25 mmHg OR

ii) IOP 26-30mmHg –commence on topical antiglaucoma drops and treat with Ozurdex

iii) IOP >30 mmHg – commence on antiglaucoma drops and review in a week. If IOP < 30mmHg, treat with Ozurdex and continue anti-glaucoma drops.

Deferred treatment: Ozurdex treatment is deferred in either arm in a planned visit if:

1. BCVA is better than 83 letters
2. IOP exceeds 30 mmHg while on Ozurdex therapy (please see retreatment criteria above).
3. Evidence of intraocular infection or severe inflammation.

The total duration of study participation is 12 months. In the intervention arm, participants will attend 4 visits – baseline, 5 months, 10 months and exit visit at 12

months. In the standard arm, the participant will be seen at baseline, 4 months and then monthly to assess the need for re-treatment. If the participant is re-treated at any time-point, the next visit will be 4 months later. All participants will attend the exit visit. There will be a one week and 8 weeks visit after the baseline and all subsequent Ozurdex injections in both treatment arms. If there is any safety concern in the opinion of the investigator, patients can be assessed at an optional post-injection assessment visit.

Selection of Subjects

Patients who attend all Medical Retina Clinics in all 5 centres who are eligible for this study based on the inclusion/exclusion criteria will be invited to the study and a patient information sheet provided. Informed consent will be obtained from the patients prior to any study procedures being performed. **In subjects where only one eye meets the inclusion criteria:** the fellow eye (non-study eye) will be monitored during the course of the study by the trial investigators and will receive the NHS standard of care of laser treatment or antiVEGF injections. **In subjects where both eyes meet the inclusion criteria:** the eye with the better visual acuity will be included in the study and become the study eye, unless patient decides otherwise. The fellow eye (non-study eye) will be treated in accordance with macular laser or antiVEGF therapy as part of the NHS standard of care, and will continue to be monitored by the study investigators throughout the study and receive further treatment if required in accordance with the standard guidelines for treating diabetic eye disease. It is expected that at least 10 eligible subjects would be seen per trial site per week, i.e. at least 500 per year of whom approx 50% would agree to enrol in the study.

Study centres

This is a multicentre study – 5 centres

Inclusion criteria

9. Subjects of either sex aged 18 years or over

10. Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following will be considered to be sufficient evidence that diabetes is present:

    i. Current regular use of insulin for the treatment of diabetes

    ii. Current regular use of oral anti-hyperglycaemic agents for the treatment of diabetes

    iii. Documented diabetes by ADA and/or WHO criteria (see Procedures Manual for Diagnosis of Diabetes)

11. Best corrected visual acuity in the study eye between ≥34 and ≤73 ETDRS letters tested as per protocol (appendix 21.1) at baseline attributable to DMO.

12. On clinical exam at baseline in the study eye, retinal thickening due to diabetic

macular oedema involving the centre of the macula and OCT central subfield > 300 microns (Spectralis) despite previous therapy.

13. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs.

14. Ability to return for study visits

7. Visual acuity in fellow eye ≥ 2/60

8. Ability to give informed consent throughout the duration of the study

Exclusion Criteria

The following exclusions apply to the study eye only (i.e. they may be present for the non study eye, provided that inclusion criterion 8 is met):

1.Macular ischaemia (FAZ > 1000µm in diameter or severe perifoveal intercapillary loss on fluorescein angiography.

2.Macular oedema is considered to be due to a cause other than diabetic macular oedema. An eye should not be considered eligible if: (1) the macular oedema is considered to be related to cataract extraction or (2) clinical exam and/or OCT suggest that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal embrane) is the primary cause of the macular oedema.

3.Co-existent ocular disease: An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular oedema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, non retinal conditions, such as amblyopia).

4.An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study (e.g. vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass syndrome, etc).

5.A substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e., cataract would be reducing acuity to 6/12 or worse if eye was otherwise normal).

6.History of treatment for DMO with peribulbar or intravitreal steroids in the study eye in the past 6 months.

7. History of macular laser in study eye in the last 3 months.

8. History of antiVEGF therapy within the last 1 month.

9. Active proliferative diabetic retinopathy or rubeosis in the study eye at baseline. (Stable and treated proliferative diabetic retinopathy may be included).

10. A condition that, in the opinion of the investigator, would preclude participation in the study.

11. A past medical history of significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant

12.. Major surgery within 28 days prior to randomisation or major surgery planned during the next 12 months at baseline. Major surgery is defined as a surgical procedure that is more extensive than fine needle biopsy/aspiration, placement of a central venous access device, removal/biopsy of a skin lesion, or placement of a peripheral venous catheter.

13. Participation in an investigational trial within 30 days of randomisation that involved treatment with any drug that has not received regulatory approval at the time of study entry. Note: subjects cannot receive another investigational drug while participating in the study.

14. Pregnant or lactating women or women intending to become pregnant within the study period.

15. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 3 months or anticipated within the next 6 months following randomisation.

16. Aphakia

17. A diagnosis of glaucoma which in the opinion of a glaucoma specialist is at high risk of progression or ocular hypertension requiring at least one topical medication.

19. History of vitrectomy in study eye.

20. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or severe blepharitis. If treated these subjects can be included.

21. Known allergy to fluorescein dye or to any component of the study drug.

22. Fertile male unwilling to use contraception for the duration of the study

Contraceptive advice to women of child-bearing age and fertile males

Women of child-bearing potential will be advised to use contraception for the duration of the study. They will be advised not to deliberately become pregnant during the trial and use contraception for 3 months after the study concludes. Women who become pregnant during the trial will have the study drug immediately discontinued and will be withdrawn from the trial. Fertile males will be advised to use contraception for the duration of the trial.

Concomitant medication

1. All medication(s)/treatment(s) excluding intravitreal antiVEGF, periocular and intravitreal steroids and macular laser treatment are permitted during the trial period in the study eye of the patients.

2. The need to initiate anti-glaucoma medications or surgery if IOP ≥ 26 mmHg. Consultation with glaucoma specialist may be considered.

3. Cataract surgery for visually significant cataract during the study period is left to the discretion of the investigator. A masked grader should determine whether the cataract is

visually significant before cataract surgery is planned. Steroid and antibiotic eye drops pre-and post cataract surgery are permitted.

4. Non-study eye may be treated with steroids, laser and antiVEGF agents.

5. Pan retinal photocoagulation for retinal neovascularisation in both study and non-study eye is permitted

Recruitment

Patients who attend all Medical Retina Clinics in the 5 centres that are eligible for this study based on the inclusion/exclusion criteria will be invited to the study by the trial investigators, and doctors not directly involved in the trial may identify subjects who might be suitable for inclusion.

The study will be discussed with potential participants and they will be provided with the Patient Information Sheet. In accordance with the principles of Good Clinical Practice, participants will be given time to decide on participation in the study, and consent will not be taken at this point.

Subjects will not be paid to participate although travel costs will be reimbursed if travel expenses are agreed with the funder.

At baseline, after consent has been obtained, subjects will undergo a full medical and ophthalmic history, vision function and quality of life questionnaires, best corrected visual acuity, ophthalmic examination, HbA1C, and 4-field fundus photography, and OCT and autofluorescence.

Study procedures and schedule of assessments

Informed consent procedure

All staff taking consent will sign the green light protocol training log..

The Principal Investigator and co-investigators will take informed consent at the screening visit at the Research and treatment centre at each eye department. Informed consent will be obtained before any trial-related procedures are done. The person taking consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the CI/PI on the delegation log. A minimum interval of 24 h will be given to patients between the patient information leaflet being given and informed consent being taken.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

“Ample time” must be given for consideration by the patient before taking part. The PI, or a person delegated by the PI, must record when the patient information sheet) has been given to the patient. The Investigator or designee will explain the patients are

under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects, including those already being treated, should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

Randomisation procedures

Subjects will be randomised using the individually 1:1 into either the fixed dosing or the PRN dosing schedule of Ozurdex therapy via a bespoke web based randomisation system hosted at the King's CTU. Patients will be randomised at the level of the individual, using the method of block randomisation with randomly varying block sizes, stratified by visual acuity (<54 or ≥54) and study site. The use of randomly varying block sizes will ensure that treatment allocation does not become deterministic towards the end of each block and thus will protect pre-randomisation allocation concealment. If both eyes are eligible the eye with the better visual acuity will be entered into the randomisation process,unless patient decides otherwise. Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation. The optometrists are the visual acuity examiners and OCT technicians do the OCT scans at all visits (i.e. assessors) and both will be masked to the participant study arm. The visual acuity examiners will receive the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be refracted, but with no previous subject records or case report forms by which the subject treatment arm could be identified. Similarly, the OCT technicians will receive the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined. The subjects will be advised at enrolment that they must not discuss the study arm they are in with the OCT or Visual Acuity examiner.

Upon randomisation, patients will be given a study specific patient card, which will have the study title, product details, patient trial number and the contact details of the Principal Investigator and out of hours contact details in cases of emergency.

Emergency un-blinding

Patients are not masked of the product.

Visits and Procedures

A month is defined as 30 days in this study.

Screening assessments

Prospective subjects as defined by the inclusion/exclusion criteria will be considered for entry into this study.

Informed Consent
Demographics
Inclusion/exclusion criteria
Medical history
Concomitant medications/procedures
Physical examination
Vital signs
Pregnancy test (urine) – required for female subjects of childbearing potential
HbA1C
BCVA (manifest refraction) (OU)
IOP measurement (OU)
OCT (OU)
Autofluorescence (OU)
Biomicroscopy (includes lens grading) (OU)
4 field retinal photographs
Fluorescein angiography (OU)
Patient-reported outcomes assessment NEI-VFQ-25, RetDQoL, RetTSQ
Randomisation
700 µg DEX PS DDS placement
Query for adverse events
Postinjection safety monitoring call <5 days after DEX PS DDS placement

Subsequent assessments- Fixed dosing arm

The participants in the fixed dosing arm will be assessed subsequently at month 5 and 10.

Concomitant medications/procedures
BCVA open aperture (OU)
IOP measurement (OU)

OCT (SE)

Biomicroscopy (includes lens grading) (OU)

700 µg DEX PS DDS placement

Query for adverse events

Postinjection safety monitoring call within 5 days after DEX PS DDS placement

Subsequent assessments- PRN dosing arm

Participants in this arm are reviewed monthly until re-treatment criteria is met. If treated, the next review will be at 4 months post-injection and then the participants are reviewed monthly until the next re-treatment. This cycle will continue until exit visit.

The following assessments will be done in these visits

Concomitant medications/procedures

BCVA open aperture(OU)

IOP measurement (OU)

OCT (SE)

Biomicroscopy (includes lens grading) (OU)

700 µg DEX PS DDS placement

Query for adverse events

Postinjection safety monitoring call within 5 days after DEX PS DDS placement

Exit visit (12 months)

Concomitant medications/procedures

Physical examination

Vital signs

Pregnancy test (urine) – required for female subjects of childbearing potential

HbA1C

BCVA (manifest refraction) (OU) IOP measurement (OU)

OCT (OU)

Autofluorescence (OU)

Biomicroscopy (includes lens grading) (OU)

Macular Steroes and 4 field retinal photographs

Fluorescein angiography (OU)

Patient-reported outcomes assessment NEI-VFQ-25, RetDQoL, RetTSQ

Query for adverse events

Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and well being of subjects during the study period. Unscheduled visit case report forms (CRFs) should be completed for each unscheduled visit. For all parameters not measured, indicate “Not Done”and sign and date the forms as appropriate.

Flowchart of study assessments:

Standard: PRN dosing arm

	Baseline (Day 0)	Treatment Of OZURDEX	4 M (120 days)	5 M (150 days)	6 M (180 days)	7 M (210 days)	8 M (240 days)	9 M (270 days)	10 M (300 days)	11 M (330 days)	12 M (360 days)
Assessment Window		(+ 7 days from baseline)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)
Informed Consent	x										
Blood Pressure	x										x
HbA1c	x										x
Pregnancy test (females of child bearing potential)	x										x
BCVA (refraction 0, 12 months)	x		x	x	x	x	x	x	x	x	x
Ophthalmic examination	x		x	x	x	x	x	x	x	x	x
IOP	x		x	x	x	x	x	x	x	x	x
LOCS II	x		x	x	x	x	x	x	x	x	x
4 field stereo photos	x										x
OCT	x		x	x	x	x	x	x	x	x	x
Autofluorescence	x										x
Fluorescein angiography	x										x
VFQ-25	x										x
RetDQoL	x										x
RetTSQ	x										x
***OZURDEX INJECTION**	x	x	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+/-	
Adverse Events			x	x	x	x	x	x	x	x	x
POST INJECTION SAFETY MONITORING CALL		X (+5days)	x (+5days)	x (+5days)	X (+5days)	X (+5days)	x (+5days)	X (+5days)	x (+5days)	x (+5days)	

* Treatment of Ozurdex injection should be given no later than +7 days after baseline assessments

If Treatment with Ozurdex is performed, the next visit will be at 4 month.

(+/- = if reinjection criteria met) A post-injection VA and IOP check should be done 1 week and 8 weeks after any Ozurdex injection. Visit window after baseline is ± 7 days

Intervention: Fixed Dosing Arm

	Baseline (Day 0)	Treatment of OZURDEX	5 M (150 days)	10 M (300 days)	12 M (360 days)
Assessment Window		(+ 7 days from baseline)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)
Informed Consent	x				
Blood Pressure	x				x
HbA1c	x				x
Pregnancy test (females of child bearing potential)	x				x
BCVA (refraction 0, 12 months)	x		x	x	x
Ophthalmic examination	x		x	x	x
IOP	x		x	x	x
LOCS II	x		x	x	x
4 field stereo photos	x				x
OCT	x		x	x	x
Autofluorescence	x				x
Fluorescein angiography	x				x
VFQ-25	x				x
RetDQoL	x				x
RetTSQ	x				x
OZURDEX INJECTION	x	X	x	x	
Adverse Events			x	x	x
POST INJECTION SAFETY MONITORING CALL		x (+5days)	x (+5days)	x (+5days)	x (+5days)

*Treatment of Ozurdex injection should be given no later than +7 days after baseline assessments
A post-injection VA and IOP check should be done 1 week and 8 weeks after any Ozurdex injection.
Visit window after baseline is ± 7 days

Laboratory procedures

Laboratory test results will be forwarded to the local labs at study site for HbA1C for all participants and pregnancy test (urine test) in child-bearing women.

Radiology or other procedures

NA

Definition of end of trial

Last patient last follow-up visit will be defined as the date of end of the trial.

Discontinuation/withdrawal of participants and 'stopping rules'

Patients will be discontinued from taking the study drug if:

- The patient develops a clinically significant medical condition that prevents continuous treatment within the study.
- The patient develops a potentially life threatening condition.
- The patient moves out of the area and is unable to return for assessments.

Withdrawn patients will not be replaced. Reasons for withdrawal and any follow-up information collected with timing.

Name and description of all drugs used in the trial

Name and description of each IMP

Intravitreal Ozurdex (700 µg Dexamethasone Posterior Segment Drug Delivery System is licensed for intravitreal use for macular oedema secondary to retinal vein occlusion but not for DMO.

See Summary of Product Characteristics.

Source of IMPs including placebo

Ozurdex will be supplied by Allergan, principal place of business being Castlebar Road, Westport, County Mayo, Ireland.

Accountability procedures for the investigation product(s), including the placebo(s) and comparator(s), if any.

The hospital pharmacy will be responsible for drug accountability. All used/unused IMP(s) that are dispensed should be returned to the trial pharmacist. They will be responsible for maintaining & updating the drug accountability log, in each hospital pharmacy file. Drug destruction will be conducted, once agreed by the sponsor and in accordance to local pharmacy practice, and this will be documented on the drug destruction log in the hospital pharmacy file.

Route of administration, dosage, dosage regimen, and treatment period(s) of the IMPs.

Dosage: Both treatment arms will receive intravitreal Ozurdex 700µg at all treatment time-points.

Dosage regimen: In the intervention arm (fixed dosing) mandated dose of intravitreal Ozurdex is given at baseline, 5 and 10 months.

In the standard (PRN dosing), re-treatment with Ozurdex is given after the baseline injection if retreatment criteria are met provided the interval between two consecutive injections should exceed 16 weeks. Re-treatment with Ozurdex is indicated in this arm if the following criteria are met:

Re-treatment criteria

1. CST exceeds 300 µm AND
2. i) IOP ≤ 25 mmHg OR

ii) IOP 26-30mmHg –commence on topical antiglaucoma drops and treat with Ozurdex

iii) IOP >30 mmHg – commence on antiglaucoma drops and review in a week. If IOP < 30mmHg, treat with Ozurdex and continue anti-glaucoma drops.

Deferred treatment: Ozurdex treatment is deferred in either arm in a planned visit if:

1. BCVA is better than 83 letters
2. IOP exceeds 30 mmHg while on Ozurdex therapy (please see retreatment criteria above).
3. Evidence of intraocular or extraocular infection or severe inflammation.

Dose modifications

None

Assessment of compliance

Not applicable.

Post-trial IMP arrangements

Any unused excess IMP will be returned to manufacturer.

Post-injection topical antibiotics will be prescribed as per local practice.

Patients will return to standard NHS care post-trial.

PHARMCOVIGILANCE/SAFETY REPORTING

Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose

	administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*

Term	**Definition**
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.

Term	Definition
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

Recording adverse events

All adverse events (AEs) will be recorded in the medical records and CRF following consent until the patient has completed their 12 month visit. AEs will include expected ocular events i.e. development of visually significant cataract or retinal neovascularization in both the study and non-study eye and the development of macular oedema in the non- study eye.

Assessments of Adverse Events

Category	Definition
Mild	The adverse event does not interfere with the subjects daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the subjects routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Each AE will be assessed for the severity criteria above.

Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	*There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.*
Probably:	*There is evidence to suggest a causal relationship, and the influence of other factors is unlikely*
Possibly	*There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).*
Unlikely	*There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).*
Not related	*There is no evidence of any causal relationship.*
Not Assessable	*Unable to assess on information available.*

Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the Investigator Brochure (or SPC if Licensed IMP) **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP)

The reference document to be used to assess expectedness against the IMP is the current SPC and current literature for Ozurdex The protocol will be used as the reference document to assess disease related and/or procedural expected events. The SPC will be checked regularly by the Sponsor and PI to ensure the latest version is being used. All copies of the SPC will be kept and made available in the TMF.

Seriousness
Seriousness is defined in section 8.1

Procedures for recording and reporting Serious Adverse Events

All SAEs will be recorded in the subject's hospital notes and the CRF.

SAEs that are rare (but expected events), related to the intravitreal procedure will be recorded but are not immediately reportable to the sponsor, These are as follows:

i. post injection endophthalmitis
ii. intraocular pressure of $\geq$ 45 mmHg
iii. acute post injection visual loss $\geq$ 30 ETDRS letter (post injection here is defined as within 30 minutes of the injection)
iv. sight-threatening adverse event: e.g. central retinal vein occlusion, retinal detachment, sterile endophthalmitis
v. Visually significant cataract is an AE and if cataract surgery is done, then it is an SAE and any hospitalization for planned cataract surgery will not be reported immediately to the sponsor but will be recorded in the medical notes and CRF.

These SAEs will not be reported to sponsor immediately but will be recorded in the medical notes and CRF.

Any SARs (SAEs related to IMP) that are expected in line with the SPC for Ozurdex will again be recorded as above, but are not immediately reportable to the sponsor. Please see section 8.15for expected events.

For all other SAE/SARs, the Chief or Principal Investigator will complete the sponsor's serious adverse event formand send to the sponsor within 24 hours of his / her becoming aware of the event. The form will be scanned and emailed to the sponsor on the following email address: Pharmacovigilance@moorfields.nhs.uk The Chief or Principal Investigator will respond to any SAE/SAR queries raised by the sponsor as soon as possible.

All SUSARs must be notified to the sponsor immediately (or at least within 24 hours

All AEs and SAEs will be discussed at the DMC. The DMC will review the accruing trial data and on-going safety issues. If there are any issues that need further action, these will be escalated to the Trial Steering Committee who will then decide whether the study continues, terminates or if any substantial changes to the protocol are required.

Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event.

Reporting SUSARs

The sponsor will notify the main REC, MHRA and Investigators of all SUSARs. A copy of the reports will be sent to the RMC and DMC.

SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after being reported to the sponsor. All other SUSARs must be reported to the REC and MHRA within 15 days after being reported to the sponsor.

Management of key ocular adverse events

Cataract:
Cataract surgery for visually significant cataract during the study period is left to the discretion of the investigator. A masked grader should determine whether the cataract is visually significant before cataract surgery is planned
Raised intraocular pressure:
i. if IOP > 26 - 30mmHg , then a topical anti-glaucoma medication is started (or a further treatment added if the patient is already taking one) before an Ozurdex injection. This does not apply to the post Ozurdex injection IOP checks. The medication will be recorded on the concomitant medication pages of the CRF.
ii. if IOP > 30mmHg at any IOP check then a topical anti-glaucoma medication is started (or a further treatment added if the patient is already taking one) and review in a week. If IOP < 30mmHg, treat with Ozurdex and continue anti-glaucoma drops.

iii. if IOP >30mmHg on 3 topical medications then a specialist glaucoma opinion should be sought
iv. The IOP is checked after 30 minutes after Ozurdex injection and if the IOP is raised (> 30mmHg) it is repeated every 15 minutes until it has fallen to < 30mmHg. If the IOP remains persistently elevated (>30mmHg) it can be treated with systemic or topical medication at the Investigators' discretion.

Other Ocular AEs

Postoperative infective endopthalmitis will be managed according to the standard Moorfields practice i.e. immediate anterior chamber and intravitreal samples for gram stain and culture and intravitreal antiobiotics

Post injection retinal tear will be managed by appropriate laser therapy but established retinal detachment will be referred to the on-call Vitreo-Retinal Service

Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with a Development Safety Update Report (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

Annual progress reports

An annual progress report (APR) will be submitted to the main REC within 30 days of the anniversary date on which the favorable opinion was given, and annually until the trial is declared ended.
The Principal Investigator will prepare the APR.

Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach 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 sponsor will notify the MHRA and REC in writing of any serious breach of –
(a) the conditions and principles of GCP in connection with that trial;
(b) or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Research Management Committee (RMC) will be notified immediately of any case where the above definition applies during the trial conduct phase.

Contraindications of Ozurdex:

- Hypersensitivity to the active substance or to any of the excipients.
- Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Pregnancy and Lactation
- Advanced glaucoma which cannot be adequately controlled by medicinal products alone.

Adverse reactions related to intravitreal injections:

Endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment.

Adverse reactions related to the drug:

Use of corticosteroids may produce **posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections.**

The prevalence of **conjunctival haemorrhage** in patients with non-infectious uveitis of the posterior segment appears to be higher compared with BRVO/CRVO. This could be attributable to the intravitreous injection procedure or to concomitant

use of topical and/or systemic corticosteroid or Non-steroidal anti-inflammatory medications. No treatment is required since spontaneous resolution occurs.

As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. Of the patients experiencing an increase of IOP of ≥10 mmHg from baseline, the greatest proportion showed this IOP increase at around 60 days following an injection. Therefore, regular monitoring of IOP, irrespective of baseline IOP, is required and any elevation should be managed appropriately post-injection as needed. **Patients of less than 45 years of age** with macular oedema following Retinal Vein Occlusion or inflammation of the posterior segment of the eye presenting as non-infectious uveitis are more likely to experience increases in IOP.

Other warnings and precautions

Corticosteroids should be **used cautiously** in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*.

The safety and efficacy of Ozurdex administered to **both eyes** concurrently have not been studied. Therefore administration to both eyes concurrently is **not recommended.**

Ozurdex has not been studied in **aphakic** patients Therefore Ozurdex should be used **with caution** in these patients.

Ozurdex has not been studied in patients with macular oedema secondary to RVO with **significant retinal ischemia**. Therefore Ozurdex is not recommended.

Anti-coagulant therapy was used in 1.7% of patients receiving Ozurdex; there were no reports of hemorrhagic adverse events in these patients. Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with Ozurdex (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%). Ozurdex should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

Table 1. Adverse reactions– BRVO/CRVO

System organ class	**Frequency**	**Adverse reaction**
Nervous system	common	Headache

disorders		
Eye disorders	very common	Intraocular pressure increased, conjunctival haemorrhage*
	common	Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*
	uncommon	Retinal tear*, anterior chamber flare*

* Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant

c) Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. During the initial treatment period, 0.7 % (3/421) of the patients who received OZURDEX required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2 % (1/423) with sham.

The adverse reaction profile of 341 patients analysed following a second injection of Ozurdex, was similar to that following the first injection. A total of 54 % of patients experienced at least one adverse reaction. The incidence of increased IOP(24.9 %) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. The overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

Uveitis

a) The clinical safety of Ozurdex in patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis, has been assessed in a single, multicentre, masked, randomised study .

A total of 77 patients were randomised to receive Ozurdex and 76 to receive Sham. A total of 73 patients (95%) randomised and treated with Ozurdex completed the 26-week study.

The most frequently reported adverse reactions in the study eye of patients who received Ozurdex were conjunctival haemorrhage (30.3%), increased intraocular pressure (25.0%) and cataract (11.8%).

b) The following adverse reactions, considered related to Ozurdex treatment were reported during the Phase III clinical trial.

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) adverse reactions are presented according to MedDRA System organ class in Table 2. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse reactions - Uveitis

System organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Migraine
Eye disorders	Very common	Increased intraocular pressure, cataract, conjunctival haemorrhage*
	Common	Retinal detachment, Myodesopsia, vitreous opacities, blepharitis, sclera hyperaemia*, visual impairment, abnormal sensation in the eye*, eyelid pruritis.

* Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant

Post-Marketing Experience

The following adverse reaction has been identified from post-marketing experience with Ozurdex:

Eye disorders Endophthalmitis (injection related)

Pregnancy

Ozurdex is contraindicated in pregnancy so female patients will have a pregnancy test at screening. Women of child-bearing potential will be advised to use contraception for the duration of the study. They will be advised not to deliberately become pregnant during the trial and use contraception for 3 months after the study concludes. Women who become pregnant during the trial will have the study drug immediately discontinued and will be withdrawn from the trial. Fertile males will be advised to use contraception for the duration of the trial.

Data management and quality assurance

9.1Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

9.2Data collection tools and source document identification

Case report forms will be designed and produced by the investigator, according to KCL data management template. The final version will be approved by the sponsor. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.

Data Item	Source Document and Location
Date of PIS given; consent date and procedure	Medical Notes and CRF
Study patient number	Medical Notes and CRF
Study visit date	Medical Notes and CRF
Demographics	CRF
Study Eye selection	Medical Notes and CRF
Questionnaires	Worksheet and CRF

BCVA	Worksheet and CRF
Colour photographs and FFA	Machine and CRF
OCT and Autofluorescence	Machine and CRF
Medical history	Medical Notes and Concomitant medications in CRF
Ophthalmic Examination	CRF
HbA1C	Medical Notes and CRF
AEs and SAEs	Medical Notes
Study drug start and stop dates	Medical Notes
Drug Dispensing	Pharmacy file
ICF	Original in ISF and copy in Medical Notes
Withdrawal dates and reasons	Medical Notes

'It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

9.3Data handling and analysis

Case Report Forms with data from each visit will be entered by the Data Entry Team within 7 days of a patient visit to the study database. Baseline data will be entered prior to randomisation. Once entered, data is automatically uploaded to the database server within KCL. All primary outcome data entered to the study database will be source data verified to check for transcription errors. The King's Clinical Trials Unit will program and host the trial data entry system (InferMed MACRO software). At the end of the study, exported data will be retained by the Chief Investigator for at least 7 years. The data will be analysed by Medical Statistician, who will be a collaborator in publications. The data collection will adhere to the Data Protection Act 1998. No patient identifiable data will be entered to the study database.

Record keeping and archiving

All site files will be retained until end of study and then be sent for archiving at the Sponsor's request.

Statistical Considerations

Medical Statistician is involved in trial design and will be involved in data analysis.

Endpoints

11.1.1Primary endpoints

Primary end point is the difference between arms in the change from baseline in best corrected visual acuity at 12 months.

11.1.2Secondary endpoints at 12 months

1. Difference between arms in proportion of patients with improvement of BCVA (gain of 10 ETDRS letters or more)
2. Difference between arms in proportion of patients with stabilization of BCVA (loss of less than 15 ETDRS letters)
3. Difference between arms in change from baseline in central retinal thickness as measured by OCT
4. Difference between arms in change from baseline in each domain and composite scores of the National Eye Institute Visual function questionnaire (VFQ-25), RetTSQ and RetDQoL.
5. Difference between arms in changes in morphological characteristics of diabetic macular oedema on OCT.
6. Difference between arms in changes in foveal avascular zone parameters and ETDRS grade of retinopathy at month 12.
7. Difference between arms in number of treatments.
8. Difference between arms in changes in distribution of BCVA change from baseline in 5 categories: a) ≥15 letters improvement b) ≥ 5 letters and < 15 letter improvement c) no change (i.e. ≥ -4 and ≤4 letters d) ≥5 letters and <15 letters worsening and e) ≥15 letters worsening.
9. Difference between arms in adverse events.

Further exploratory analyses may be done as new data emerges.

11.2Sample size and recruitment

11.2.1Sample size calculation

If there is truly no difference between fixed and variable dosing groups and a SD of 9 letters, then 84 patients are required to be 83% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of 5 letters. Allowing for 10% missing data, 100 patients will be randomized. The SD is based on the Ranibizumab study in the RESOLVE study. The non-inferiority margin of 5 letters is used in the CATT study and is commonly accepted margin. Mean average change from baseline to 12 months in PLACID is 5 letters.

11.2.2Planned recruitment rate

We plan to recruit 4-5 patients per month per site. So recruitment will be completed by 6 months. This is based on our previous recruitment rates for studies for the same indication.

11.2.3 Statistical analysis plan

One database lock will occur when all patients have either completed the study or discontinued from the study prematurely. At the time of database lock the randomisation code will be unmasked. A detailed analysis plan will be approved prior to database lock.

Three analysis populations are defined: intent-to-treat (ITT), per protocol (PP), and a safety population (SP).

The ITT population is defined as all patients who were randomised at the baseline visit. The ITT population will be used for all efficacy analyses and summaries baseline characteristics based on the treatment assigned per the randomisation schedule. The PP population is defined as the subset of the ITT population who was treated and had no major protocol violations. This population will be determined before database lock. In the analysis using the PP population, patients will be analyzed based on the treatment actually received.

The safety population is defined as all randomized patients who received the study treatment and will be used for the analysis of all safety parameters. The safety analysis will be based on the actual treatment the patients receive.

11.2.4Summary of baseline data and flow of patients

Patient characteristics obtained during the baseline visit will be listed and summarized by treatment group and overall. This will include descriptive statistics for continuous variables and frequencies and proportions for categorical variables..

A tabulation of concomitant medications by treatment group will be performed for the study.

A CONSORT flow-diagram will be displayed to provide the details on the number of eligible patients identified for the trial, the number consenting and the number randomised. Also a breakdown for each group of the numbers of participants assigned, receiving the intended treatment, completing the study protocol, and analysed for the primary outcome.

11.2.5Primary endpoint analysis

The primary outcome will be the difference in mean change in baseline best corrected ETDRS visual acuity (BCVA) letter score at 12 months between the two arms. Non inferiority will be assessed by comparing the 95% confidence interval for

the difference in means to the inferiority margin adjusting for baseline. Analysis will primarily be on an intention to treat basis, supported by a per protocol analysis.

11.2.6Secondary endpoint analysis

All the secondary end-points will be analysed, regardless of the significance of the primary end-point. Secondary analyses will be considered as hypothesis generating rather than providing firm conclusions. Analyses of secondary outcomes will primarily be unadjusted and reported as differences in means or proportions for continuous and binary data respectively. All tests will be two-sided and, at the 12-month primary time-point, will be assessed at the 5% significance level.

11.2.7Sensitivity and other planned analyses

Although a low rate of missing data is anticipated, a sensitivity analysis will be undertaken using baseline and available reported measurements of the primary outcome using a linear mixed effects model with full polynomial terms over time by arm. This will provide an estimate of the treatment difference at the 12-month time-point under a missing at random assumption.

Adverse events will be summarized as treatment emergent signs and symptoms using the pre-randomization period as baseline. All safety data, including AEs, deaths, discontinuation, concomitant medications and HbA1C will be listed and summarized using mean, SD, and percentiles for continuous random variables, and frequencies and percentages for categorical variables.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

11.3Randomisation

Randomisation will be via a bespoke web based randomisation system hosted at the King's CTU. Patients will be randomised at the level of the individual, using the method of block randomisation with randomly varying block sizes, stratified by study site. The use of randomly varying block sizes will ensure that treatment allocation does not become deterministic towards the end of each block and thus will protect pre-randomisation allocation concealment. If both eyes are eligible, the eye with the better visual acuity will be entered into the randomisation process, unless patient decides otherwise Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation. The optometrists are the visual acuity examiners and OCT technicians do the OCT scans at all visits (i.e. assessors) and both will be masked to the participant study arm. The visual acuity examiners will receive the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be

refracted, but with no previous subject records or case report forms by which the subject treatment arm could be identified. Similarly, the OCT technicians will receive the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined. The subjects will be advised at enrolment that they must not discuss the study arm they are in with the OCT or Visual Acuity examiner.

11.4Interim analysis: None

11.5Other statistical considerations

An interim analyses may be conducted if it is deemed necessary by the DMC.

12 Name of Committees involved in trial

All AEs and SAEs will be discussed by the Data Monitoring Committee (DMC) and they will review the accruing trial data and on-going safety issues. If there are any issues that need further action, these will be escalated to the Trial Steering Committee (TSC) who will then decide whether the study continues, terminates or if any substantial changes to the protocol are required.

13Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

14Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the sites can enrol patients into the trial, the Chief Investigator or designee must apply for Site Specific Assessment from Trust Research & Development (R&D) and be granted written NHS R&D approval. It is the responsibility of the Chief Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 8.13 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI and sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply a summary report of the clinical trial to the MHRA and main REC within 1 year after the end of the trial.

15Monitoring plan for the trial

The trial will be monitored according to the monitoring plan agreed by the Sponsor. Authorized representatives of the Sponsor or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

16Finance

The study is funded by a grant from Allergan Pharmaceuticals17Insurance

NHS Indemnity covers the Sponsor's liability for the design, management and conduct of this study.

The Sponsor has not made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

18. Publication policy

Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centres, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the Sponsor.

Statement of compliance

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

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APPENDICES

Protocol for Measuring Best Corrected Visual Acuity

Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation. The visual acuity examiners will receive the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be refracted, but with no previous subject records or case report forms by which the subject treatment arm could be identified. The subjects will be advised at enrolment that they must not discuss the study arm they are in with the Visual Acuity examiner.

Refracted best corrected visual acuity is performed at baseline, and 12 months in all subjects in both eyes. Open aperture best corrected visual acuity is recorded in both eyes at all other assessments. VA is always measured in the study eye first, then the fellow eye. If cataract surgery is done during the study, refraction should be repeated in the next trial visit and this new refraction should be used in all follow-up visits until 12 months when refraction will be repeated in both eyes.

Initial VA Measurement:

At the baseline visit, initial VA is measured, whilst the subject is wearing his/her own distance glasses or unaided (if subject doesn't have distance glasses), using ETDRS Chart R. At all follow-up visits refraction found during the previous study refraction will be used. The fellow eye is lightly patched with a tissue. If the initial acuity is less than 20/200 refraction should occur at 1 metre.

Retinoscopy

Retinoscopy should be performed using a light / duochrome chart at 6m.

Subjective Refraction

Subjective refraction should be carried out according to the methods routinely employed by the Optometry Departmentlocally. The subjective refraction is performed at 4m using a ETDRS chart with the room lights off.

Final VA Measurement

VA in the study eye first is always measured first, then the fellow eye. The subject is instructed that the chart contains letters only and no numbers. If the subject forgets this during the course of the examination, they should be reminded that the chart contains no numbers and asked for a letter instead of the number. The subject is advised that there are 5 letters on each line, and that they should attempt to read the line from left to right. The examiner must not point at any letters or read any letters out loud during the

test. It is acceptable to briefly point at a line, should the subject have difficulty finding the next line. The subject should be instructed to read the letters slowly, about one letter per second. The subject should be encouraged to guess any letters that are difficult to read, and be instructed to make a definite decision. If the subject is unable to identify a certain letter they should tell the examiner that they are moving on to the next letter along the line. If the subject incorrectly identifies a letter and then proceeds to read the next letter, s/he cannot go back and correct the mistake later. It is permissible to allow correction as long as the subject has not started to read the next letter aloud. The subject should be asked (and encouraged) to move on to the next line, as long as they manage to correctly identify at least one letter on the previous line.

With the subject wearing the best correction in the trial frame, the eye not being tested is occluded with a standard occluder in the trial frame, or with a tissue/patch behind the frame, if the subject moves his/her head a lot to use eccentric fixation.

Following refraction the best VA's are measured at 4m using ETDRS Chart 1 for the right eye and Chart 2 for the left eye. During the VA measurements the room lights need to be **switched off**.

The subject is asked to look at the smallest line they can read on the ETDRS. Follow the instructions for recording the final ETDRS-score and VA outlined below.

ETDRS Score

Each letter correctly identified is circled on the visual acuity form. Any letters read incorrectly are deleted, and letters, for which no guess has been made, are left unmarked. Each correct letter scores one point. The total for each line is recorded in the right-hand column (max.5), and the scores for each line added at the bottom. If the score is 20 or more, then 30 points are added automatically and the final VA score is recorded. If the total score is less then 20, then the acuity should be tested at 1m. The chart is moved so that it is exactly 1m from the subject. Before testing at 1m, +0.75DS should be added to the sphere in the back cell of the trial frame. If the subject feels that this makes their vision worse, then it should be removed again. Only the first six lines are read at 1m, giving a maximum score of 30. The approximate Snellen equivalent is also recorded in feet. The Acuity recorded is the smallest line with 1 or no error

Testing for Count Fingers

If the subject's VA is so poor that s/he cannot correctly identify any letters on the chart when tested at one meter, then test for Count Fingers. The eye not being tested should be completely occluded with a patch. A light must be shone from behind the subject's head at the examiner's hand. The examiner holds the hand two feet in front of the subject's face and presents an arbitrary number of fingers in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the subject

correctly identifies 3 of the 5 presentations, then count fingers vision is noted. If not, then the subject must be tested for hand movements.

Testing for Hand Movements

The eye not being tested is occluded with a patch. A light must be shone from behind the subject's head at the examiner's hand. The examiner's hand should be moved two feet in front of the subject with all fingers spread out. The hand should be moved either horizontally or vertically at a constant speed of approx. one back and forth movement per second. The subject is asked to watch the examiner's hand and respond to the question "in which direction is my hand moving?" The examiner should not explain that it will be moving either from side to side or up and down! Correct answers at four out of five presentations suggest that hand movement vision is present. If not, then light perception should be tested for.

Testing for Light Perception

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope should be focused at 1meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the eye at least four times, and the subject should be asked to respond when they see the light. If the examiner is convinced that the subject perceives light, vision should be recorded as "Light Perception". If not, vision should be recorded as "No Light Perception".

LOCS II Lens Grading Protocol

The presence and severity of nuclear, cortical and posterior subcapsular lens opacities will be measured during slit lamp examination using standardized photographs and the Lens Opacities Classification System II (LOCS II)

Pupils should be dilated

Slit Lamp examination with 10X Magnification

The appropriate codes are used separately for right and left eye

Nuclear Colour	
NC0	<N1 standard
NCI	Similar to N1standard
NCII	>N1 standard
Nuclear Standard	
N0	Clear Nucleus
NI	Early degree of nuclear opacification

NII	Moderately advance nuclear opacification
NIII	Advanced nuclear opacification and browning
Cortical Standard	
C0	Clear lens devoid of aggregated dots flecks vacuoles and waterclefts
Ctr	Minimal degree of cortical opacification and or mini spoke formation
CI	More extensive opacification with small minispokes
CII	Cortical spoking that obscures more than 2 full quadrants
CIII	Opacification that obscures about 50% of the intrapupillary zone
CIV	Advanced opacification filling about 90% of the interpupillary zone
Posterior subcapsular cataract	
P0	Clear posterior capsule
P1	Cataract filling about 3% of the area of the posterior capsule
PII	About 30% opacification of the area of the posterior capsule
PIII	About 50% opacification of the area of the posterior capsule

4 Field Colour Fundus Photography

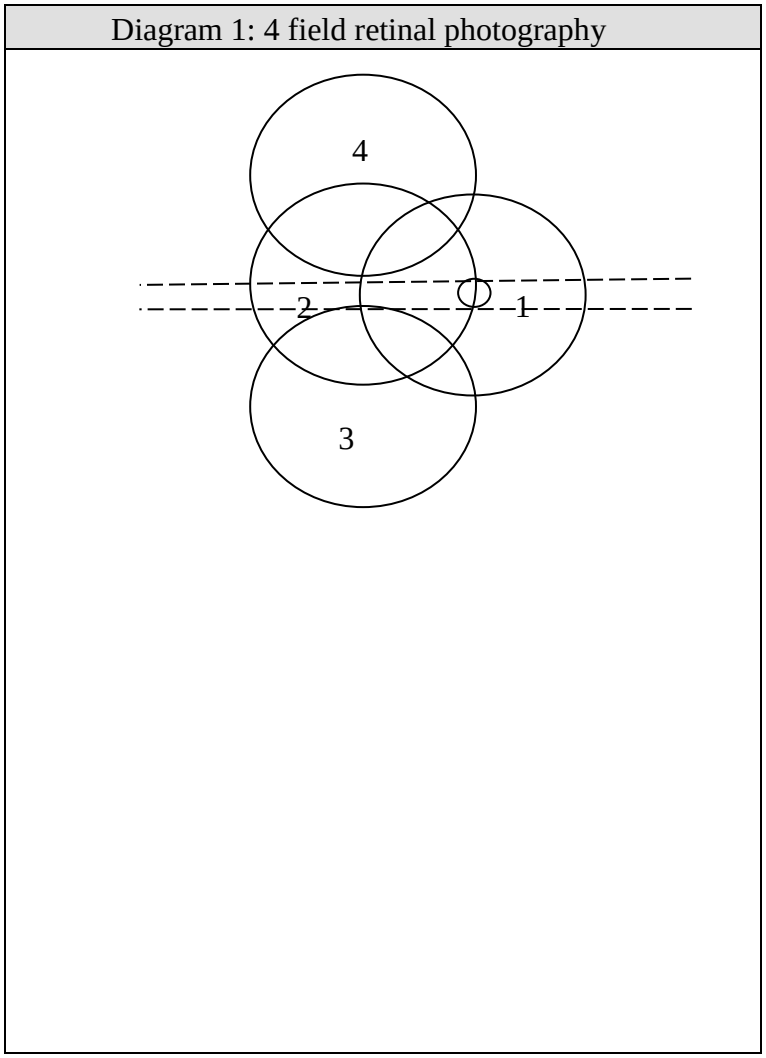
AIM

To grade the degree of retinopathy in all subjects at baseline and final follow-up at 12 months.

METHOD:

4 stereo photographs must be obtained as follows: (diag 1)

Diagram 1: 4 field retinal photography



5. Centred on the disc with the temporal border on the macula
6. Centred on the macula with the nasal border over the centre of the disc.
7. Directly inferior to the macula with the inferior border in line with the superior edge of the disc.
8. Directly superior to the macula with the superior border in line with the inferior edge of the disc.

SAMPLING TIME
4 field stereo photos will be taken at baseline and at exit (12months)

MINIMAL CRITERIA
Fields 1 and 2 must be in focus

GRADING
To be performed by the investigator.

Fundus Fluorescein Angiography (FFA)

FFA will be performed in all subjects at baseline to determine the degree of macular ischaemia and therefore study suitability. FFA will be repeated in all subjects at 12 months to assess the degree of macular ischaemia in terms of greatest linear diameter of FAZ, area of the FAZ and degree of perifoveal capillary dropout. Minimal Criteria for acceptable FFA quality are that early phase angiography must be performed to allow grading of macular ischaemia. The macula must be in focus. For digital capture the following fields are preferable. Field 2 - Macula: Centre the macula at the intersection of the cross hairs in the ocular. It is important that good even illumination is used at all times and that the flash settings are kept at the correct levels to ensure this.

The timing for the procedure is as follows: -

1. Before the injection of the fluorescein dye,
2. Position camera on F2 of eye to be treated (index eye) prior to injection.
3. 5ml of fluorescein is injected rapidly (in less than 5secs if possible).

Early or Transit Phase

1. The 1st photograph of F2 of the index eye is taken at the start of the injection and the 2nd at the end of the injection. The purpose of this is to document the time taken to inject the dye.
2. 15-30 sec (F2 index eye): - Take a rapid series of about 10-16 exposures at intervals of about 1 to 2 seconds.

Mid Phase

5. 30 - 45 seconds: F2 of the index eye
6. 50 seconds - 1 min: F2 of the fellow eye
7. 2 min: F2 of the index and fellow eye
8. 2½-3 min: F2 of index eye

Late Phase

- 5 min: F2 of index eye and fellow eye

Grading Macular Ischaemia

Grading of macular ischaemia is based on an early phase / mid-phase photograph.

It is determined by 3 grading systems. These are the maximum diameter of the foveal avascular zone, area of the foveal avascular zone and degree of perifoveal capillary dropout according to the ETDRS standard photo of moderate capillary loss.

DIAMETER OF THE FAZ

The greatest linear dimension of the foveal avascular zone will be documented with the measuring tool on the Topcon system. This will be done by the study investigators.

AREA OF FAZ

This is measured by hand drawing a line around the edge of the foveal avascular zone and using the automated area measuring tool on the Topcon software to calculate the FAZ area.

ETDRS PERIFOVEAL CAPILLARY DROPOUT

Intercapillary distance will be judged against standard ETDRS photograph of moderate perifoveal capillary dropout.

Normal : normal perifoveal intercapillary distance

Questionable : slightly abnormal perifoveal intercapillary distance

Mild : definitely abnormal but better than moderate standard ETDRS photograph

Moderate : equal to moderate ETDRS standard photograph

Severe : worse than moderate ETDRS standard photograph.

Spectral Domain Optical Coherence Tomography

Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation . The OCT technicians will receive the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined. Optical Coherence Tomography (OCT) will be assessed on both eyes at baseline and month 12. Only study eye will be assessed at every other visit. These assessments will be performed by an OCT certified clinical trial unit technician. OCT imaging will be performed using the Spectralis OCT machine.

Investigators and the OCT grading technicians will use OCT to diagnose and to monitor presence or absence of significant macular oedema. The macular thickness measurement determines whether subjects randomised to Ozurdex PRN dosing therapy receive a further injection that day; this occurs if CST $\geq$ 300µm in the central ETDRS subfield.

OCT parameters will include:

Resolution mode:	High Speed
ART:	≥20 (the setting is 24)
Pattern:	(49 scans, 20°, 120µ separation)
Centred:	Anatomical fovea

Procedure for intravitreal Ozurdex injection

1. Injection is performed under sterile conditions in a designated treatment room. The procedure will be explained to the subject who will then lie supine. Prior to injection, a preloaded injection of Ozurdex will be supplied from Pharmacy Clinical Trial stock.
2. A local anaesthetic injection (2% lignocaine) will be given to the bulbar conjunctiva.
3. The eye is disinfected. This involves scrubbing the eyelids, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. It is important to ensure that the eyelid margins and lashes are swabbed, procedure is performed in a systematic fashion and that povidone iodide is used to irrigate the conjunctival sac.
4. The skin is then dried and a drape applied and a lid speculum is inserted to retract the eyelids
5. The subject is instructed to direct their eyes upward and medially. The preferred site of injection is inferotemporally. The conjunctiva and sclera can be held with a tooth forceps to minimise risk of the eye moving during the injection.
6. With calipers, 4.0mm is measured posterior to the limbus in the phakic patent and 3.5mm in the pseudophakic subject. Ozurdex is then injected at this site, through the pars plana in the inferotemporal quadrant, into the vitreous cavity, aiming towards the centre of the globe. The injection should be delivered slowly. The needle should then be removed slowly to ensure the implant is in the eye. If possible a sterile cotton tip applicator should be placed on the injection site to minimise reflux.
7. A drop of topical antibiotic is placed in the fornix at the end of the procedure. The subject will be monitored with a finger count test by the injecting physician immediately (within 90 seconds) after injection of Ozurdex.
8. The IOP is checked after 30 minutes and if the IOP is raised (> 30mmHg) it is repeated every 15 minutes until it has fallen to < 30mmHg. If the IOP remains persistently elevated (>30mmHg) it can be treated with systemic or topical medication at the Investigators' discretion.
9. Following injection, topical antibiotic is instilled into the eye 4 times a day for 4 days and the subject is advised to contact the Clinical Trials Unit immediately should any symptoms suggestive of infection develop after intravitreal injection.

VIII. Summary of protocol amendments

Protocol Version	Date	Substantial/ Minor	Details of amendment
1.1		Original application	Original application only provisional opinion given by ethics
2.0	18-10-2012	Original application	Incorporated changes requested by MHRA
3.0	19-10-2012	Original application	Approved by ethics and MHRA for final use
3.0 (1)	19-10-2012	Minor	- Schedule of events includes +7 day window - Section 9.2 consent form to be stored in ISF rather than TMF
3.0 (2)	19-10-2012	Minor	- Fax number for Racheal Yoon removed, tel number same as fax.
3.0 (3)	19-10-2012	Minor	- Schedule of events table, new column added treatment of Ozurdex. - Explanation that baseline treatment should be given no more than 7 days after assessments done.
4.0	01-05-2013	substantial	- addition of Brighton as new site
4.1	02-07-2013	Minor	- Section 6.1, addition of person delegated by PI to record when PIS given
4.2	16-07-2013	Substantial	no change to main protocol so version number not changed to 5.0 at this stage. - Change of PI at Brighton site
5.0	26-07-2013	Substantial – but no funding sent to MHRA for their review so never approved nor circulated for use	Section 11.3 (randomisation): - Change "worse" to "better" in the following paragraph: "If both eyes are eligible, the eye with the worse visual acuity will be entered into the randomisation process." - Section 11.2.1 (sample size calculation): Need to change power from 80% to 83% - Section 1 (summary): Significance level of tests: Change this to say: "The primary outcome will be tested using a 1-sided p-value, and presented with a 1-sided 95% confidence interval (or equivalently a 2-sided 90% confidence interval). All other statistical tests will use a 2-sided p-value of 0.05 and be presented with a 2-sided 95% confidence interval, unless otherwise specified." -Primary efficacy: Change "A 2-sided 95% confidence interval will be estimated…" to "A 1-sided 95% confidence interval (or equivalently a 2-sided 90% confidence interval) will be estimated…" & Typo of Analyses of Variance changes to Analysis - Section 11.2.4 (summary of baseline data and flow of patients):Need to remove the following text: "Statistical comparisons will be performed mine whether treatment groups are comparable with respect to prognostic factors at baseline. For continuous variables, such as

			age, analysis of variance (ANOVA) techniques will be applied. For discrete variables such as gender, a chi-square test or Fisher's exact test will be applied." - Section 11.3 – Randomisation - The typo of worse to better. - Section 5.3 – Concomitant medication- Addition of, cataract surgery will be done for visually significant cataract as graded by a masked grader - Section 21.1 – Measuring VA - Open aperture replaces pin-hole in protocol for vision. - Section 21. 1 - If cataract surgery is done during the study, refraction should be repeated in the next trial visit and this new refraction should be used in all follow-up visits until 12 months when refraction will be repeated in both eyes. - Section 8.3 – Procedure for reporting SAEs - Change of fax number for reporting SAEs so it's in line with the SOP. - Section 5.0 – Selection of Subjects – Addition of sentence showing patient choice on better or worse eye inclusion. - Section 6.2 – Randomisation Processes – Addition of sentence showing patient choice on better or worse eye inclusion - Section 11.3 – Randomisation - Addition of sentence showing patient choice on better or worse eye inclusion. - Section 7.4 - Route of administration, dosage, dosage regimen, and treatment period(s) of the IMPs – removal of text not. "injection if retreatment criteria are met provided the interval between two consecutive injections should not exceed 16 weeks
6.0	11-10-2013	Substantial – details of 5 as well as new details re-sent to MHRA and new details only in next column sent to Ethics	- Section 2.2 - IMP, updated date of SmPC to 28/05/2013 - Section 8 –Pharmacovigilence reporting updated - Schedule of events table, new row added to include post injection safety phone call
7.0		Substantial (several minor changes throughout the protocol sponsor felt it best to submit as substantial due to the vast amount)	- several grammatical errors updated throughout whole of protocol - structure changed to whole of protocol so all unified - corrections in places to confirm fixed dosing is intervention arm and PRN dosing is the standard arm - section 8 – pharmacovigilence several updates/ clarifications

IX. Case Report Forms – Version 1.0

Registration Form

Participant Informed Consent:

1.	**Date participant received Patient Information Sheet and first discussed the study:**	/ /
2.	**Date participant signed written consent form:**	/ /
3.	**Date of first trial-related procedure:**	/ /

Demographic Data:

4.	**Participant initials**	
5.	**Participant date of birth (dd/mm/yyyy)**	/ /

6.	**Gender**	**0**	**Male**
		1	**Female**

7.	**Ethnicity?**	**0**	**White / Caucasian**	
		1	**Black or African**	
		2	**South Asian**	
		3	**Other**	**Go to question 8**

8.	**If other please specify**	
9.	**Year of diagnosis of diabetes: (yyyy)**	
10.	**Duration of diabetic macular oedema in study eye: (mm/yyyy partial date)**	/

11.	**Type of diabetes:**	**0**	**Type 1**
		1	**Type 2 on insulin**
		2	**Type 2 on tablets**

Participant Status

1.	**Attendance**	**1**	**PRN patient attended**
		2	**PRN patient, not attended as injection < 4 months ago**
		3	**PRN patient, not attended due to non-compliance**
		4	**PRN patient, withdrawn from trial, refusing further data collection**
		5	**PRN patient, deceased**
		6	**Fixed dose patient, attended**
		7	**Fixed dose patient, not attended as visit not due**
		8	**Fixed dose patient, not attended due to non-compliance**
		9	**Fixed dose patient, withdrawn from trial, refusing further data collection**
		10	**Fixed dose patient, deceased**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

2.	**Does the patient require re-treatment?**	**1**	**PRN patient: Yes, treat at this visit**
		2	**PRN patient: Yes but not given (protocol deviation)**
		3	**PRN patient: No, less than 4 months since last treatment**
		4	**PRN patient: No, injection not required**
		5	**Fixed dose patient: Yes, treat at this visit (M5 or M10)**
		6	**Fixed dose patient: Yes, but pressure too high (M5 or M10)**
		7	**Fixed dose patient: Yes but not given (protocol deviation)**
		8	**Fixed dose patient: No, not due treatment at this visit**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

If there have been any new Adverse Events, please record in Adverse Events Log

If any medications have been started, stopped or doses changed, please record in Concomitant Medication Form

Eligibility Form

INCLUSION CRITERIA:
The following criteria MUST be answered YES for participant to be included in the trial:

1.	**> 18 yrs**	**1**	**Yes**
		0	**No**

2.	**Diabetes Mellitus (type 1 or 2)**	**1**	**Yes**
		0	**No**

3.	**DMO on OCT involving fovea**	**1**	**Yes**
		0	**No**

4.	**VA decrease due to DMO**	**1**	**Yes**
		0	**No**

5.	**BCVA ≥ 34 and ≤ 73**	**1**	**Yes**
		0	**No**

6.	**OCT Central subfield thickness ≥ 300**	**1**	**Yes**
		0	**No**

7.	**Media clarity study eye**	**1**	**Yes**
		0	**No**

8.	**Ability to return for study visits**	**1**	**Yes**
		0	**No**

9.	**Visual acuity fellow eye ≥2/60**	**1**	**Yes**
		0	**No**

If any of the above criteria is answered NO, the participant is NOT eligible for the trial and must not be included in the study.

EXCLUSION CRITERIA:
The following criteria MUST be answered NO for the participant to be included in the trial (except where NA is appropriate):

1.	**Macular ischaemia FAZ >1000um**	**1**	**Yes**
		0	**No**
		777	**N/A**

2.	**Ocular – Macular oedema not due to DMO/ significant cataract that could interfere with visual outcome**	**1**	**Yes**
		0	**No**
		777	**N/A**

3.	**Co-existent ocular disease that may affect visual acuity**	**1**	**Yes**
		0	**No**
		777	**N/A**

4.	**Renal failure requiring dialysis or kidney transplant**	**1**	**Yes**
		0	**No**
		777	**N/A**

5.	**Major surgery within 28 days prior randomization or planned during the next 12 months**	**1**	**Yes**
		0	**No**
		777	**N/A**

6.	**Glaucoma with IOP>30mmHg or OHT on at least 1 medication/ glaucoma surgery**	**1**	**Yes**
		0	**No**
		777	**N/A**
7.	**Active PDR**	**1**	**Yes**
		0	**No**
		777	**N/A**
8.	**Aphakia**	**1**	**Yes**
		0	**No**
		777	**N/A**
9.	**Macular laser to study eye within 3 months**	**1**	**Yes**
		0	**No**
		777	**N/A**
10.	**Anti-VEGF within 1 month**	**1**	**Yes**
		0	**No**
		777	**N/A**
11.	**External ocular infection should be treated first before inclusion.**	**1**	**Yes**
		0	**No**
		777	**N/A**
12.	**Periocular or intravitreal steroids Ozurdex within 6 months**	**1**	**Yes**
		0	**No**
		777	**N/A**
13.	**Cataract surgery within 3 months or anticipated within 6 months**	**1**	**Yes**
		0	**No**
		777	**N/A**
14.	**Vitrectomy in study eye**	**1**	**Yes**
		0	**No**
		777	**N/A**
15.	**Allergy to study medication/ fluorescein**	**1**	**Yes**
		0	**No**
		777	**N/A**
16.	**Female patients – pregnant/nursing/planning a pregnancy/ childbearing not on contraception**	**1**	**Yes**
		0	**No**
		777	**N/A**
17.	**Fertile male unwilling for contraception**	**1**	**Yes**
		0	**No**
		777	**N/A**
18.	**Simultaneous participation in another CTIMP study**	**1**	**Yes**
		0	**No**
		777	**N/A**

Vital Signs

1.	**Blood pressure**	☐☐☐/☐☐☐ **mmHg**	
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

2.	**Pregnancy tests (urine) for female participants – results:**	**1**	**Positive**
		0	**Negative**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

3.	**HbA1C Result:**	☐☐.☐	
		77.7	*Not available or not applicable*
		88.8	*Not done*
		99.9	*Unknown*

Randomization

1.	**Does the participant still satisfy the inclusion and exclusion criteria to date and are they still willing to proceed in the trial?**	**1**	**Yes**
		0	**No**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

2.	**Patient randomised?**	**1**	**Yes**	**Go to question 1**
		0	**No**	

3.	**Date Randomised:**	/ / **Day Month Year**

4.	**Treatment allocation**	**1**	**PRN dosing**
		0	**Fixed dosing**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

5.	**Reason not randomised:**	**1**	**Withdrawal of consent**
		2	**Clinical deterioration**
		3	**Unable to locate / contact participant**
		4	**Death**
		5	**Other, please specify**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

6.	**Other please specify:**		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

OPHTHALMIC HISTORY

Is there any relevant significant ophthalmic history?

Code	Condition	*Yes	No
1	Cataract		
2	Pseudophakia		
3	Glaucoma		

Code	System	*Yes	No
4	Previous other eye surgery		
5	Optic nerve disorders		
6	Other		

*If ***YES*** for any of the above, enter the code for each condition in the boxes below, giving further details (including dates) and state if the condition is currently or potentially active. If giving details of surgery please specify the underlying cause. Use a separate line for each condition.

7. Code	8. Condition	9. Dates

PRIOR DMO TREATMENT:

10.	PRIOR DMO TREATMENT?	**1**	**Yes**	**If yes complete question 11**
		0	**No, none**	**If no complete question 18**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

11.	Macular laser	**1**	**Yes**	**If yes complete question 12 & 13**
		0	**No**	**If no complete question 14**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

12.	If yes, number of Macular laser treatments to date		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

13.	Time since last Macular laser?	**1**	**< 1year**
		2	**≥ 1 year**
		3	**NA**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

14.	AntiVEGF	**1**	**Yes**	**If yes complete question 15**
		0	**No**	**If no complete question 16**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

15.	If yes, number of AntiVEGF treatments to date		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

16.	Steroids	**1**	**Yes**	**If yes complete question 17**
		0	**No**	**If no complete question 18**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

17.	If yes, number of Steroids treatments to date		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

PRIOR Pan retinal photocoagulation (PRP)

18.	**Prior PRP?**	**1**	**Yes**	**If yes complete question 19**
		0	**No, none**	**If no end of form**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

19.	**Time since last PRP?**	**1**	**< 1year**
		2	**≥ 1 year**
		3	**NA**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

MEDICAL HISTORY

Is there any relevant significant medical history in the following systems?

Code	System	*Yes	No
1	Cardiovascular		
2	Respiratory		
3	Hepatic		
4	Gastro-intestinal		
5	Genito-urinary		
6	Endocrine		
7	Haematological		
8	Musculo-skeletal		
9	Neoplasia		

Code	System	*Yes	No
10	Neurological		
11	Psychiatric		
12	Immunological		
13	Dermatological		
14	Allergies		
15	Ophthalmological		
16	Ear, nose, throat		
17	Other, please specify details below		

*If ***YES*** for any of the above, enter the code for each condition in the boxes below, giving further details (including dates) and state if the condition is currently or potentially active. If giving details of surgery please specify the underlying cause. Use a separate line for each condition.

Code	Medical Condition	Dates

BCVA

1.	**Was Best Corrected Visual Acuity performed (refracted)?**	**1**	**Yes**	**If yes complete question 2**
		0	**No**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

2.	**Date of BCVA:** **(dd/mm/yyyy)**	| | / | | / | | | | | **Day Month Year**
		If missing please enter 01/01/1900

RESULTS

3R.	**RIGHT EYE: ETDRS LETTERS:**	| | |	**4L.**	**LEFT EYE: ETDRS LETTERS:**	| | |

Study Eye - *N.b. In bilateral cases that meet the inclusion/exclusion criteria, the eye with the better presenting vision (assessed by BCVA) will be recruited unless that eye shows signs of irreversible damage due to central atrophy, epiretinal membrane or the oedema is due to any other cause.*			
5.	**Study Eye: (Circle one)**	**1**	**Right eye**
		2	**Left eye**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

TONOMETRY & OPHTHALMIC EXAM

1.	**Were Tonometry & Ophthalmic exams performed?**	**1**	**Yes**	If yes complete question 2
		0	**No**	

2.	**Date of Tonometry:**	/ / Day Month Year

3R.	**RIGHT EYE: Time (24hr clock):**	.		**20L.**	**LEFT EYE: Time (24hr clock):**	.	
4R.	**RIGHT EYE: IOP (mmHg):**			**21L.**	**LEFT EYE: IOP (mmHg):**		
5R.	**RIGHT EYE: Eye structure, lids**	**1**	Normal	**22L.**	**LEFT EYE: Eye structure, lids**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)
6R.	**RIGHT EYE: Eye structure (lids) findings**			**23L.**	**LEFT EYE: Eye structure (lids) findings**		
7R.	**RIGHT EYE: Eye structure, cornea**	**1**	Normal	**24L.**	**LEFT EYE: Eye structure, cornea**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)
8R.	**RIGHT EYE: Eye structure (cornea) findings**			**25L.**	**LEFT EYE: Eye structure (cornea) findings**		
9R.	**RIGHT EYE: Eye structure, conjunctiva**	**1**	Normal	**26L.**	**LEFT EYE: Eye structure, conjunctiva**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)

10R.	**RIGHT EYE:** **Eye structure (conjunctiva) findings**	

27L.	**LEFT EYE:** **Eye structure (conjunctiva) findings**	

11R.	**RIGHT EYE:** **Eye structure, iris**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

28L.	**LEFT EYE:** **Eye structure, iris**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

12R.	**RIGHT EYE:** **Eye structure (iris) findings**	

29L.	**LEFT EYE:** **Eye structure (iris) findings**	

13R.	**RIGHT EYE:** **Eye structure, anterior chamber**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

30L.	**LEFT EYE:** **Eye structure, anterior chamber**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

14R.	**RIGHT EYE:** **Eye structure (anterior chamber) findings**	

31L.	**LEFT EYE:** **Eye structure (anterior chamber) findings**	

15R.	**RIGHT EYE:** **Cataract (nuclear)**	**1**	N0	☐
		2	NI	☐
		3	NII	☐
		4	NIII	☐

32L.	**LEFT EYE:** **Cataract (nuclear)**	**1**	N0	☐
		2	NI	☐
		3	NII	☐
		4	NIII	☐

16R.	**RIGHT EYE:** **Cataract (cortical)**	**1**	C0	☐
		2	CTR	☐
		3	CI	☐
		4	CII	☐
		5	CIII	☐
		6	CIV	☐

33L.	**LEFT EYE:** **Cataract (cortical)**	**1**	C0	☐
		2	CTR	☐
		3	CI	☐
		4	CII	☐
		5	CIII	☐
		6	CIV	☐

17R.	**RIGHT EYE:** **Cataract (posterior subcapsular)**	**1**	P0	**34L.**	**LEFT EYE:** **Cataract (posterior subcapsular)**	**1**	P0
		2	PI			**2**	PI
		3	PII			**3**	PII
		4	PIII			**4**	PIII

18R.	**RIGHT EYE:** **Pseudophakia**	**1**	Yes	**35L.**	**LEFT EYE:** **Pseudophakia**	**1**	Yes
		0	No			**0**	No

19R.	**RIGHT EYE:** **Yag Capsultomy**	**1**	Yes	**36L.**	**LEFT EYE:** **Yag Capsultomy**	**1**	Yes
		0	No			**0**	No

INFLAMMATION ASSESSMENT

37R.	**RIGHT EYE:** **Eye structure, anterior chamber flare**	**0**	0	**41L.**	**LEFT EYE:** **Eye structure, anterior chamber flare**	**0**	0
		1	Trace			**1**	Trace
		2	1+			**2**	1+
		3	2+			**3**	2+
		4	3+			**4**	3+
		5	4+			**5**	4+

38R.	**RIGHT EYE:** **Eye structure, anterior chamber cells**	**0**	0	**42L.**	**LEFT EYE:** **Eye structure, anterior chamber cells**	**0**	0
		1	Trace			**1**	Trace
		2	1+			**2**	1+
		3	2+			**3**	2+
		4	3+			**4**	3+
		5	4+			**5**	4+

39R.	**RIGHT EYE:** **Eye structure, Vitreous cells**	**0**	0	**43L.**	**LEFT EYE:** **Eye structure, Vitreous cells**	**0**	0
		1	Trace			**1**	Trace
		2	1+			**2**	1+
		3	2+			**3**	2+
		4	3+			**4**	3+
		5	4+			**5**	4+

40R.	**RIGHT EYE:** **Eye structure, Vitreal Haemorrhage density**	**0**	0	**44L.**	**LEFT EYE:** **Eye structure, Vitreal Haemorrhage density**	**0**	0
		1	Trace			**1**	Trace
		2	1+			**2**	1+
		3	2+			**3**	2+
		4	3+			**4**	3+
		5	4+			**5**	4+

OPHTHALMOSCOPY

45R.	**RIGHT EYE:** **Eye structure, Retina (including peripheral)**	**1**	Normal	**58L.**	**LEFT EYE:** **Eye structure, Retina (including peripheral)**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)
46R.	**RIGHT EYE:** **Eye structure Retina (including peripheral) findings**			**59L.**	**LEFT EYE:** **Eye structure Retina (including peripheral) findings**		
47R.	**RIGHT EYE:** **Eye structure, Macula**	**1**	Normal	**60L.**	**LEFT EYE:** **Eye structure, Macula**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)
48R.	**RIGHT EYE:** **Eye structure (Macula) findings**			**61L.**	**LEFT EYE:** **Eye structure (Macula) findings**		
49R.	**RIGHT EYE:** **Eye structure, Choroid**	**1**	Normal	**62L.**	**LEFT EYE:** **Eye structure, Choroid**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)
50R.	**RIGHT EYE:** **Eye structure (Choroid) findings**			**63L.**	**LEFT EYE:** **Eye structure (Choroid) findings**		
51R.	**RIGHT EYE:** **Eye structure, Optic nerve**	**1**	Normal	**64L.**	**LEFT EYE:** **Eye structure, Optic nerve**	**1**	Normal
		2	Clinically insignificant abnormality			**2**	Clinically insignificant abnormality
		3	Clinically significant abnormality (specify in Findings)			**3**	Clinically significant abnormality (specify in Findings)

52R.	**RIGHT EYE:** **Eye structure (Optic nerve) findings**	

65L.	**LEFT EYE:** **Eye structure (Optic nerve) findings**	

53R.	**RIGHT EYE:** **Eye structure, Cup to disc ratio**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

66L.	**LEFT EYE:** **Eye structure, Cup to disc ratio**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

54R.	**RIGHT EYE:** **Eye structure (Cup to disc ratio) findings**	

67L.	**LEFT EYE:** **Eye structure (Cup to disc ratio) findings**	

55R.	**RIGHT EYE:** **Eye structure, Other, please specify**	

68L.	**LEFT EYE:** **Eye structure, Other, please specify**	

56R.	**RIGHT EYE:** **Eye structure, Other**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

69L.	**LEFT EYE:** **Eye structure, Other**	**1**	Normal	☐
		2	Clinically insignificant abnormality	☐
		3	Clinically significant abnormality (specify in Findings)	☐

57R.	**RIGHT EYE:** **Eye structure (Other) findings**	

70L.	**LEFT EYE:** **Eye structure (Other) findings**	

71.	**Does the study eye require cataract surgery?**	**1**	**Yes**
		0	**No**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

72.	**Does the study eye need PRP?**	**1**	**Yes**
		0	**No**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

73.	**Does the fellow eye require cataract surgery?**	**1**	**Yes**
		0	**No**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

74.	**Does the fellow eye need PRP?**	**1**	**Yes**
		0	**No**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

OCT Evaluation

1.	**Was OCT performed?**	**1**	**Yes**	**If yes complete question 2**
		0	**No**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

2.	**Date of OCT:**	/ / **Day Month Year** ***If missing please enter 01/01/1900***

OCT EVALUATION:

3R.	**RIGHT EYE: Central Retinal Thickness (µm):**		**7L.**	**LEFT EYE: Central Retinal Thickness (µm):**	
4R.	**RIGHT EYE: Central subfield thickness (µm):**		**8L.**	**LEFT EYE: Central subfield thickness (µm):**	
5R.	**RIGHT EYE: Total volume (mm^3):**	.	**9L**	**LEFT EYE: Total volume (mm^3):**	.

6R.	**RIGHT EYE: No. of ETDRS zones with thickness more than 300µm**	**1**	**1**	**10L**	**LEFT EYE: No. of ETDRS zones with thickness more than 300µm**	**1**	**1**
		2	**2**			**2**	**2**
		3	**3**			**3**	**3**
		4	**4**			**4**	**4**
		5	**5**			**5**	**5**
		6	**6**			**6**	**6**
		7	**7**			**7**	**7**
		8	**8**			**8**	**8**
		9	**9**			**9**	**9**

VITREOMACULAR TRACTION (VMT):

11R.	**RIGHT EYE: Vitreomacular traction (VMT):**	**1**	**Absent VMT**	**12L**	**LEFT EYE: Vitreomacular traction (VMT):**	**1**	**Absent VMT**
		2	**Definite VMT**			**2**	**Definite VMT**
		3	**Partial Vitreomacular separation**			**3**	**Partial Vitreomacular separation**
		4	**Posterior Vitreous Detachment**			**4**	**Posterior Vitreous Detachment**

INTRARETINAL DIFFUSE OEDEMA:

13R.	**RIGHT EYE: Intraretinal diffuse oedema:**	**1**	**Absent**	**14L**	**LEFT EYE: Intraretinal diffuse oedema:**	**1**	**Absent**
		2	**Definite**			**2**	**Definite**

INTRARETINAL CYSTS:

15R.	**RIGHT EYE: Intraretinal cysts:**	**1**	**Absent**	**16L**	**LEFT EYE: Intraretinal cysts:**	**1**	**Absent**
		2	**Definite**			**2**	**Definite**

SUBRETINAL FLUID:

17R.	**RIGHT EYE: Subretinal fluid:**	**1**	**Absent**	**18L**	**LEFT EYE: Subretinal fluid:**	**1**	**Absent**
		2	**Definite**			**2**	**Definite**

Autofluorescence Evaluation

1.	**Was autofluorescence performed?**	**1**	**Yes**	**If yes complete question 2**
		0	**No**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

2.	**Date of autofluorescence:**	__ / __ / ____ **Day Month Year**
		If missing please enter 01/01/1900

AUTOFLUORESENCE EVALUATION: HYPER AUTOFLUORESENCE

3R.	**RIGHT EYE: Was Hyper autofluorescence present?**	**1**	Yes	Go to 4	**5L.**	**LEFT EYE: Was Hyper autofluorescence present?**	**1**	**Yes**	Go to 6
		0	**No**	Go to 5			**0**	**No**	Go to 7

4R.	**RIGHT EYE: Total area of Hyper autofluorescence size (µm)**	____.__	**6L.**	**LEFT EYE: Total area of Hyper autofluorescence size (µm)**	____.__

AUTOFLUORESENCE EVALUATION: HYPO AUTOFLUORESENCE

7R.	**RIGHT EYE: Was Hypo autofluorescence present?**	**1**	Yes	Go to 8	**9L.**	**LEFT EYE: Was Hypo autofluorescence present?**	**1**	**Yes**	Go to 10
		0	**No**	Go to 9			**0**	**No**	End form

8R.	**RIGHT EYE: Total area of Hypo autofluorescence size (µm)**	____.__	**10L**	**LEFT EYE: Total area of Hypo autofluorescence size (µm)**	____.__

FFA & Colour Photographs

1.	**Was Fluorescein Angiography performed?**	**1**	**Yes**	**If yes complete question 2**
		0	**No**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

2.	**Date of FFA:** **(dd/mm/yyyy)**	/ /
		If missing please enter 01/01/1900

3R.	**RIGHT EYE:** **Grade of retinopathy**	**0**	**Mild**	**10L.**	**LEFT EYE:** **Grade of retinopathy**	**0**	**Mild**
		1	**Moderate**			**1**	**Moderate**
		2	**Severe**			**2**	**Severe**
		3	**Treated PDR**			**3**	**Treated PDR**
4R.	**RIGHT EYE:** **Macular Ischaemia (FAZ >1000µm):** **[See Exclusion]**	**1**	**Yes**	**11L.**	**LEFT EYE:** **Macular Ischaemia (FAZ >1000µm):** **[See Exclusion]**	**1**	**Yes**
		0	**No**			**0**	**No**
5R.	**RIGHT EYE:** **Macular Oedema**	**0**	**Focal predominant**	**12L.**	**LEFT EYE:** **Macular Oedema**	**0**	**Focal predominant**
		1	**Diffuse predominant**			**1**	**Diffuse predominant**
6R.	**RIGHT EYE:** **Hard Exudates in central 6mm fovea**	**1**	**Yes**	**13L.**	**LEFT EYE:** **Hard Exudates in central 6mm fovea**	**1**	**Yes**
		0	**No**			**0**	**No**
7R.	**RIGHT EYE:** **Active PDR** [See Exclusion]	**1**	**Yes**	**14L.**	**LEFT EYE:** **Active PDR** [See Exclusion]	**1**	**Yes**
		0	**No**			**0**	**No**
8R.	**RIGHT EYE:** **FAZ area (mm2)**	.		**15L.**	**LEFT EYE:** **FAZ area (mm2)**	.	
9R.	**RIGHT EYE:** **FAZ GLD (mm)**			**16L.**	**LEFT EYE:** **FAZ GLD (mm)**		

Retinopathy-Dependent Quality of Life
RETDQOL

This questionnaire asks about your quality of life – in other words, how good or bad you feel your life to be. Please put an "X" in the box that best indicates your response for each item. What we would like to know is how you feel about your life now.

00a.	**In general, my present quality of life is:**	**1**	**excellent**
		2	**very good**
		3	**good**
		4	**neither good nor bad**
		5	**bad**
		6	**very bad**
		7	**extremely bad**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

Now we would like to know how your quality of life is affected by your diabetic eye problems – the eye problems often caused by diabetes.
We want you to think about your diabetic eye problems, not your diabetes itself.

00b.	**If I did not have diabetic eye problems, my quality of life would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

Please respond to the more specific statements on the following pages.
For each aspect of life described, you will find two parts:
For part (a) put an "X" in one box to show how diabetic eye problems affect this aspect of your life.
For part (b) put an "X" in one box to show how important this aspect of your life is to your quality of life.

01a.	**If I did not have diabetic eye problems, I could handle my household tasks:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

01b.	**Handling my household tasks is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

02a.	**If I did not have diabetic eye problems, I could handle my personal affairs (letters, bills, etc):**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

02b.	**Handling my personal affairs is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

03a.	**If I did not have diabetic eye problems, my experience of shopping would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

03b.	**My experience of shopping is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

04a.	**If I did not have diabetic eye problems, my feelings about the future (e.g. worries, hopes) would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

04b.	**My feelings about the future are:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

05a.	**If I did not have diabetic eye problems, my feelings about past medical care and/or self-care (e.g. anger or regret) would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

05b.	**My feelings about the past are:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

06.	**Are you currently working, looking for work or would you like to work?**	**1**	**Yes**	**Go to 6a**
		0	**No**	**Go to 7**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

06a.	**If I did not have diabetic eye problems, my working life would be:**	**1**	**very much better**	
		2	**much better**	
		3	**a little better**	
		4	**the same**	
		5	**Worse**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

06b.	**For me, having a working life is:**	**1**	**very important**	
		2	**Important**	
		3	**somewhat important**	
		4	**not at all important**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

07.	**Do you have, or would you like to have, a close personal relationship (e.g. husband / wife, partner)?**	**1**	**Yes**	**Go to 7a**
		0	**No**	**Go to 8**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

07a.	**If I did not have diabetic eye problems, my closest personal relationship would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

07b.	**For me, having a close personal relationship is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

08.	**Do you have any family / relatives?**	**1**	**Yes**	**Go to 8a**
		0	**No**	**Go to 9**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

08a.	**If I did not have diabetic eye problems, my family life would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

08b.	**My family life is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

09a.	**If I did not have diabetic eye problems, my friendships and social life would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

09b.	**My friendships and social life are:**	**1**	**very important**	
		2	**important**	
		3	**somewhat important**	
		4	**not at all important**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

10a.	**If I did not have diabetic eye problems, I could do things for others as I wish:**	**1**	**very much better**	
		2	**much better**	
		3	**a little better**	
		4	**the same**	
		5	**worse**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

10b.	**For me, doing things for others is:**	**1**	**very important**	
		2	**important**	
		3	**somewhat important**	
		4	**not at all important**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

11a.	**If I did not have diabetic eye problems, I could get out and about (e.g. on foot, or by car, bus or train):**	**1**	**very much better**	
		2	**much better**	
		3	**a little better**	
		4	**the same**	
		5	**worse**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

11b.	**For me, getting out and about is:**	**1**	**very important**	
		2	**important**	
		3	**somewhat important**	
		4	**not at all important**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

12.	**Do you ever go on holiday or want to go on holiday?**	**1**	**Yes**	**Go to 12a**
		0	**No**	**Go to 13**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

12a.	**If I did not have diabetic eye problems, my holidays would be:**	**1**	**very much better**	
		2	**much better**	
		3	**a little better**	
		4	**the same**	
		5	**worse**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

12b.	**For me, holidays are:**	**1**	**very important**	
		2	**important**	
		3	**somewhat important**	
		4	**not at all important**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

13a.	**If I did not have diabetic eye problems, my financial situation would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**Worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

13b.	**My financial situation is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

14a.	**If I did not have diabetic eye problems, the way people in general react to me would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

14b.	**The way people in general react to me is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

15a.	**If I did not have diabetic eye problems, my physical appearance (including clothes and grooming) would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

15b.	**My physical appearance is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

16a.	**If I did not have diabetic eye problems, physically I could do:**	**1**	**very much more**
		2	**much more**
		3	**a little more**
		4	**the same**
		5	**less**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

16b.	**For me, how much I can do physically is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

17a.	**If I did not have diabetic eye problems, I could enjoy my leisure activities and interests (e.g. reading, TV, radio, hobbies):**	**1**	**very much more**
		2	**much more**
		3	**a little more**
		4	**the same**
		5	**less**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

17b.	**My leisure activities are:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

18a.	**If I did not have diabetic eye problems, my self-confidence would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

18b.	**My self-confidence is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

19a.	**If I did not have diabetic eye problems, my motivation would be:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

19b.	**My motivation is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

20.	**Are there occasions when you wish you did not need to depend on other people?**	**1**	**Yes**	**Go to 20a**
		0	**No**	**Go to 21**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

20a.	**If I did not have diabetic eye problems, I could do things independently:**	**1**	**very much better**
		2	**much better**
		3	**a little better**
		4	**the same**
		5	**worse**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

20b.	**For me, being able to do things independently is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*

		999	*Unknown*

21a.	**If I did not have diabetic eye problems, I would have mishaps or would lose things:**	**1**	**very much less**
		2	**much less**
		3	**a little less**
		4	**the same**
		5	**more**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

21b.	**For me, not having mishaps or losing things is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

22a.	**If I did not have diabetic eye problems, the time it takes me to do things would be:**	**1**	**very much less**
		2	**much less**
		3	**a little less**
		4	**the same**
		5	**more**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

22b.	**The time it takes me to do things is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

23a.	**If I did not have diabetic eye problems, I would find taking care of my diabetes (e.g. self-testing, medication, food, exercise):**	**1**	**very much easier**
		2	**much easier**
		3	**a little easier**
		4	**the same**
		5	**more difficult**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

23b.	**Taking care of my diabetes is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

24a.	**If I did not have diabetic eye problems, I could enjoy nature:**	**1**	**very much more**
		2	**much more**
		3	**a little more**
		4	**the same**
		5	**less**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

24b.	**My enjoyment of nature is:**	**1**	**very important**
		2	**important**
		3	**somewhat important**
		4	**not at all important**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

25.	**Do your diabetic eye problems affect your quality of life in any ways that have not been covered by the questionnaire?**	**1**	**Yes**	**Go to 25a**
		0	**No**	**End form**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

If 'yes', please describe in the box provided

25a.	

Retinopathy Treatment Satisfaction Questionnaire
RETTSQ

The following questions are about your experience of treatment for your diabetic eye problems – the eye problems often caused by diabetes.

Your eye treatment includes:
- **medications (e.g. tablets, eye drops).**
- **visits to the doctor and hospital for check-ups and laser treatment or surgery.**

In this questionnaire, please:
- **think about the treatment for your diabetic eye problems, not for your diabetes itself.**
- **think about your eye treatment over the past few weeks/ months.**
- **answer each question by putting an "X" in the box next to one of the numbers from 6 to 0.**

1	**How satisfied are you with the treatment for your diabetic eye problems?**	**6**	**6. very satisfied**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very dissatisfied**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

2	**How well do you feel the treatment for your diabetic eye problems is working?**	**6**	**6. very well**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very badly**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

3	**How bothered are you by any side effects or after effects of the treatment for your diabetic eye problems?**	**6**	**6. not at all bothered**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very bothered**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

4	**How bothered are you by any discomfort or pain from the treatment for your diabetic eye problems?**	**6**	**6. not at all bothered**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very bothered**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

5	**How unpleasant do you find the treatment for your diabetic eye problems?**	**6**	**6. not at all unpleasant**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very unpleasant**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

6	**How difficult for you is the treatment for your diabetic eye problems?**	**6**	**6. very easy**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very difficult**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

7	**How apprehensive do you feel about the treatment for your diabetic eye problems?**	**6**	**6. not at all apprehensive**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very apprehensive**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

8	**How satisfied are you with the influence you have over the treatment for your diabetic eye problems?**	**6**	**6. very satisfied**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very dissatisfied**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

9	**How satisfied are you with the safety of the treatment for your diabetic eye problems?**	**6**	**6. very satisfied**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very dissatisfied**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

10	**How satisfied are you with the time taken by the treatment for your diabetic eye problems?**	**6**	**6. very satisfied**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very dissatisfied**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

11	**How satisfied are you with the information provided about the treatment for your diabetic eye problems?**	**6**	**6. very satisfied**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very dissatisfied**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

12	**Would you encourage someone else with diabetic eye problems like yours to have your kind of treatment?**	**6**	**6. yes, I would definitely encourage them**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. no, I would definitely not encourage them**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

13	**How satisfied would you be to continue or repeat the treatment for your diabetic eye problems?**	**6**	**6. very satisfied**
		5	**5.**
		4	**4.**
		3	**3.**
		2	**2.**
		1	**1.**
		0	**0. very dissatisfied**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

14	**Are there any other features of the treatment for your diabetic eye problems, causing either satisfaction or dissatisfaction, that have not been covered by the questionnaire?**	**1**	**Yes**	**Go to 15**
		0	**No**	**End form**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

If 'yes', please describe in the box provided.

15	

Visual Functioning Questionnaire
(VFQ 25 version 2000)

Instructions:
I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

PART 1 - GENERAL HEALTH AND VISION

1.	**In general, would you say your overall health is*:** **READ CATEGORIES:** **(Circle One)**	**1**	**Excellent**
		2	**Very Good**
		3	**Good**
		4	**Fair**
		5	**Poor**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

*** Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

2.	**At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?** **READ CATEGORIES:** **(Circle One)**	**1**	**Excellent**
		2	**Good**
		3	**Fair**
		4	**Poor**
		5	**Very Poor**
		6	**Completely Blind**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

3.	**How much of the time do you worry about your eyesight?** **READ CATEGORIES:** **(Circle One)**	**1**	**None of the time**
		2	**A little of the time**
		3	**Some of the time**
		4	**Most of the time**
		5	**All of the time?**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

4.	**How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:** **READ CATEGORIES:** **(Circle One)**	**1**	**None**
		2	**Mild**
		3	**Moderate**
		4	**Severe, or**
		5	**Very severe?**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5.	**How much difficulty do you have reading ordinary print in newspapers? Would you say you have:** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

6.	**How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

7.	**Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

8.	**How much difficulty do you have reading street signs or the names of stores?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

9.	**Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

10.	**Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

11.	**Because of your eyesight, how much difficulty do you have seeing how people react to things you say?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**	
		2	**A little difficulty**	
		3	**Moderate difficulty**	
		4	**Extreme difficulty**	
		5	**Stopped doing this because of your eyesight**	
		6	**Stopped doing this for other reasons or not interested in doing this**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

12.	**Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**	
		2	**A little difficulty**	
		3	**Moderate difficulty**	
		4	**Extreme difficulty**	
		5	**Stopped doing this because of your eyesight**	
		6	**Stopped doing this for other reasons or not interested in doing this**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

13.	**Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**	
		2	**A little difficulty**	
		3	**Moderate difficulty**	
		4	**Extreme difficulty**	
		5	**Stopped doing this because of your eyesight**	
		6	**Stopped doing this for other reasons or not interested in doing this**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

14.	**Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**	
		2	**A little difficulty**	
		3	**Moderate difficulty**	
		4	**Extreme difficulty**	
		5	**Stopped doing this because of your eyesight**	
		6	**Stopped doing this for other reasons or not interested in doing this**	
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

15.	**Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?** **(Circle One)**	**1**	**Yes**	**Go to 15c**
		2	**No**	**Go to 15a**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

15a.	**IF NO, ASK: Have you never driven a car or have you given up driving?** **(Circle One)**	**1**	**Never drove**	**Go to 17**
		2	**Gave up**	**Go to 15b**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

15b.	**IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?** **(Circle One)**	**1**	**Mainly eyesight**	**Go to 17**
		2	**Mainly other reasons**	**Go to 17**
		3	**Both eyesight and other reasons**	**Go to 17**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

15c.	**IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:** **(Circle One)**	**1**	**No difficulty at all**	**Go to 16**
		2	**A little difficulty**	**Go to 16**
		3	**Moderate difficulty**	**Go to 16**
		4	**Extreme difficulty**	**Go to 16**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

16.	**How much difficulty do you have driving at night? Would you say you have:** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

16a.	**How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:** **(READ CATEGORIES AS NEEDED)** **(Circle One)**	**1**	**No difficulty at all**
		2	**A little difficulty**
		3	**Moderate difficulty**
		4	**Extreme difficulty**
		5	**Stopped doing this because of your eyesight**
		6	**Stopped doing this for other reasons or not interested in doing this**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time. (READ CATEGORIES)

17.	**Do you accomplish less than you would like because of your vision?** **(Circle One)**	**1**	**All of the time**
		2	**Most of the time**
		3	**Some of the time**
		4	**A little of the time**
		5	**None of the time**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

18.	**Are you limited in how long you can work or do other activities because of your vision?** **(Circle One)**	**1**	**All of the time**
		2	**Most of the time**
		3	**Some of the time**
		4	**A little of the time**
		5	**None of the time**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

19.	**How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:** **(Circle One)**	**1**	**All of the time**
		2	**Most of the time**
		3	**Some of the time**
		4	**A little of the time**
		5	**None of the time**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

20.	**I stay home most of the time because of my eyesight.** **(Circle One)**	**1**	**Definitely true**
		2	**Mostly true**
		3	**Not sure**
		4	**Mostly false**
		5	**Definitely false**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

21.	**I feel frustrated a lot of the time because of my eyesight.** **(Circle One)**	**1**	**Definitely true**
		2	**Mostly true**
		3	**Not sure**
		4	**Mostly false**
		5	**Definitely false**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

22.	**I have much less control over what I do, because of my eyesight.** **(Circle One)**	**1**	**Definitely true**
		2	**Mostly true**
		3	**Not sure**
		4	**Mostly false**
		5	**Definitely false**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

23.	**Because of my eyesight, I have to rely too much on what other people tell me.** **(Circle One)**	**1**	**Definitely true**
		2	**Mostly true**
		3	**Not sure**
		4	**Mostly false**
		5	**Definitely false**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

24.	**I need a lot of help from others because of my eyesight.** **(Circle One)**	**1**	**Definitely true**
		2	**Mostly true**
		3	**Not sure**
		4	**Mostly false**
		5	**Definitely false**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

25.	**I worry about doing things that will embarrass myself or others, because of my eyesight.** **(Circle One)**	**1**	**Definitely true**
		2	**Mostly true**
		3	**Not sure**
		4	**Mostly false**
		5	**Definitely false**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

Injection Worksheet

1.	**Has the participant received their baseline Ozurdex injection (1x implant - 700micrograms)?**	**1**	**Yes**	
		0	**No**	**If yes complete question 2**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

2.	**If not why not:**		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

3.	**Date of Injection:**	/ / **Day Month Year**
		If missing please enter 01/01/1900

4.	**Time of Injection:**	/ **HH:MM 24 hour clock**
		If missing please enter 00:00

5.	**Initials of person performing the injection**		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

IOP – 30 MINS POST INJECTION (BOTH EYES)

6.	**Time:**	/ **HH:MM 24 hour clock**
		If missing please enter 00:00

7R.	**RIGHT EYE** (mm Hg)		**8L.**	**LEFT EYE** (mm Hg)	

IF PRESSURE ≥ 30 MM HG, TREAT ACCORDINGLY AND REPEAT IOP EVERY 15 MINUTES UNTIL <30mmHg. RECORD ON AE LOG/ CON MED LOG.

9.	**Time:**	/ **HH:MM 24 hour clock**
		If missing please enter 00:00

10R.	**RIGHT EYE** (mm Hg)		**11L.**	**LEFT EYE** (mm Hg)	

12.	**Time:**	☐☐/☐☐ **HH:MM 24 hour clock** *If missing please enter 00:00*

13R.	**RIGHT EYE** (mm Hg)	☐☐	**14L.**	**LEFT EYE** (mm Hg)	☐☐

PLEASE RECORD ANY ADVERSE EVENTS EXPERIENCED AFTER TREATMENT ON THE AE LOG

IOP – 1 WEEK POST INJECTION (BOTH EYES)

15.	**Date**	☐☐/☐☐/☐☐☐☐ **Day Month Year** *If missing please enter 01/01/1900*

16.	**Time:**	☐☐/☐☐ **HH:MM 24 hour clock** *If missing please enter 00:00*

17R.	**RIGHT EYE:** 1 week (mm Hg)	☐☐	**18L.**	**LEFT EYE:** 1 week (mm Hg)	☐☐

IOP – 8 WEEKS POST INJECTION (BOTH EYES)

19.	**Date**	☐☐/☐☐/☐☐☐☐ **Day Month Year** *If missing please enter 01/01/1900*

20.	**Time:**	☐☐/☐☐ **HH:MM 24 hour clock** *If missing please enter 00:00*

21R.	**RIGHT EYE:** 8 weeks (mm Hg)	☐☐	**22L.**	**LEFT EYE:** 8 weeks (mm Hg)	☐☐

Retreatment Injection Worksheet

1.	**Did the patient have an injection at this visit?**	**1**	**PRN patient: Yes**
		2	**PRN patient: No**
		3	**Fixed dose patient: Yes**
		4	**Fixed dose patient: No**
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

2.	**Date of Injection:** **Collect form if 1=1 or 3**	__/__/____ **Day Month Year**
		If missing please enter 01/01/1900

3.	**Time of Injection:**	__/__ **HH:MM 24 hour clock**
		If missing please enter 00:00

4.	**Initials of person performing the injection**	___	
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

IOP – 30 MINS POST INJECTION (BOTH EYES)

5.	**Time:**	__/__ **HH:MM 24 hour clock**
		If missing please enter 00:00

6R.	**RIGHT EYE:** 30 minutes (mm Hg)	__	**7L.**	**LEFT EYE:** 30 minutes (mm Hg)	__

IF PRESSURE ≥ 30 MM HG, TREAT ACCORDINGLY AND REPEAT IOP EVERY 15 MINUTES UNTIL <30mmHg. RECORD ON AE LOG/ CON MED LOG.

IOP – 1 WEEK POST INJECTION (BOTH EYES)

8.	**Date**	__/__/____ **Day Month Year**
		If missing please enter 01/01/1900

9.	**Time:**	__/__ **HH:MM 24 hour clock**
		If missing please enter 00:00

10R.	**RIGHT EYE:** 1 week (mm Hg)	__	**11L.**	**LEFT EYE:** 1 week (mm Hg)	__

IOP – 8 WEEKS POST INJECTION (BOTH EYES)		
12.	**Date**	/ / **Day Month Year** *If missing please enter 01/01/1900*
13.	**Time:**	/ **HH:MM 24 hour clock** *If missing please enter 00:00*

14R.	**RIGHT EYE:** 8 weeks (mm Hg)		**15L.**	**LEFT EYE:** 8 weeks (mm Hg)	

PLEASE RECORD ANY ADVERSE EVENTS EXPERIENCED AFTER TREATMENT ON THE AE LOG

Withdrawal Form

Please complete at the point of withdrawal, death or at the last study visit.

1.	**Has the participant withdrawn from study?**	**1**	**Yes**
		0	**No**

2.	**Date of withdrawal (dd/mm/yyyy)**	/ /	
		01/01/1900	*Unknown*

3.	**Reason for withdrawal**	**1**	**Death of participant**	
		2	**Adverse event**	
		3	**Participant no longer able to travel to centre**	
		4	**Unable to locate / contact participant**	
		5	**Other, please specify**	**Go to question 4**
		777	*Not available or not applicable*	
		888	*Not done*	
		999	*Unknown*	

4.	**If other, please specify reason for withdrawal**		
		777	*Not available or not applicable*
		888	*Not done*
		999	*Unknown*

5.	**Briefly describe the circumstances of the withdrawal**	

Concomitant Medication Form

Is this medication Ophthalmology related? Coded as: Yes = 1 No = 0	**Name of Medication** **(Brand or Generic)**	**Body system code** Coded as: 1. Cardiovascular 2. Respiratory 3. Hepatic 4. Gastro-intestinal 5. Genito-urinary 6. Endocrine 7. Haematological 8. Musculo-skeletal 9. Neoplasia 10. Neurological 11. Psychiatric 12. Immunological 13. Dermatological 14. Allergies 15. Eyes 16. Ear, nose, throat 17. Food supplement 18. Homeopathic 19. Herbal 20. Other	**Date Started** **(dd/mm/yyyy)**	**Ongoing at end of study?** **(Complete at end of study or withdrawal)** Coded as: 1. Yes 0. No 2. Not at study end	**Date Stopped** **(dd/mm/yyyy)**	**Dose**	**Units** Coded as: 1. Milligram 2. Application 3. Capsule 4. Drop 5. Gram 6. Inhaled 7. Litre 8. Microgram 9. Millilitre 10. Puff 11. Suppository 12. Tablespoon 13. Tablet 14. Teaspoon 15. Trans-dermal (patch) 16. International Units	**Frequency** Coded as: 1. Once daily 2. Twice daily 3. Three times daily 4. Four times daily 5. As required 6. Continuous 7. Other (please specify)	**If other for frequency, please specify**

Adverse Events Form

Has the participant experienced any Adverse Events since signing the Informed Consent to the trial?	YES, specify below	1	NO	0

Related to injection? Yes = 1 No = 0	Adverse Event [Diagnosis or symptom (if known) or signs/symptoms]	Body system code Coded as: 1. Cardiovascular 2. Respiratory 3. Hepatic 4. Gastro-intestinal 5. Genito-urinary 6. Endocrine 7. Haematological 8. Musculo-skeletal 9. Neoplasia 10. Neurological 11. Psychiatric 12. Immunological 13. Dermatological 14. Allergies 15. Eyes 16. Ear, nose, throat 17. Food supplement 18. Homeopathic 19. Herbal 20. Other	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Intensity Mild = 1 Moderate = 2 Severe = 3	Related to Study Intervention? Definite = 1 Probable = 2 Possible = 3 Remote = 4 None = 5	Is this a Serious Adverse Event? Yes = 1 No = 0

X. Randomisation according to sites

Moorfields Eye Hospital		Royal Wolverhampton NHS Trust	
Patient ID	**Treatment arm**	**Patient ID**	**Treatment arm**
P01001 M-A	Fixed	P02007 T-B	PRN
P01002 D-M	PRN	P02008 R-R	Fixed
P01003 S-K	PRN	P02012 N-W	PRN
P01004 R-S	Fixed	P02016 K-H	PRN
P01005 GMK	Fixed	P02017 F-E	Fixed
P01006 H-G	PRN	P02027 B-R	Fixed
P01013 S-B	PRN	P02031 M-V	Fixed
P01014 RGF	Fixed	P02038 A-M	PRN
P01015 A-E	Fixed	P02039 W-B	PRN
P01018 T-O	PRN	P02042 A-H	Fixed
P01020 M-P	Fixed	P02044 N-H	Fixed
P01026 M-T	Fixed	P02045 D-C	PRN
P01028 LFT	PRN	P02046 MSM	Fixed
P01029 N-B	PRN	P02047 K-B	PRN
P01036 H-B	PRN	P02049 W-S	Fixed
P01037 ECC	Fixed	P02050 A-P	PRN
P01041 GKM	PRN	P02052 D-S	Fixed
P01043 CVE	Fixed	P02057 K-P	PRN
P01051 T-S	PRN	P02061 J-D	Fixed
P01053 J-E	Fixed	P02063 J-M	PRN
P01054 B-B	PRN	P02077 A-K	Fixed
P01062 ASB	Fixed	P02087 S-H	PRN
P01064 A-B	Fixed	P02090 B-S	PRN
P01065 PCB	PRN	P02100 D-P	Fixed
P01067 PHD	PRN	P02101 P-C	Fixed
P01070 CSH	Fixed		
P01076 PJH	PRN		
P01079 B-K	Fixed		
P01084 SR	PRN		
P01085 BGF	Fixed		
P01088 VJD	PRN		
P01089 BAP	Fixed		

Bristol Eye Hospital		Frimley Health NHS Foundation Trust	
Patient ID	**Treatment arm**	**Patient ID**	**Treatment arm**
P03009 M-C	PRN	P04019 D-R	Fixed
P03058 d.r	Fixed	P04021 R-C	PRN
P03068 M.R	Fixed	P04022 B-M	PRN
P03075 M-G	PRN	P04023 M-J	Fixed
P03078 BQ	PRN	P04024 J-M	PRN
P03080 MT	Fixed	P04025 C-B	Fixed
P03081 G.H	PRN	P04030 S-O	Fixed
P03082 MP	Fixed	P04032 LAH	PRN
P03091 EB	PRN	P04033 RKT	Fixed
P03102 CS	PRN	P04034 W-M	PRN
Brighton and Sussex NHS Trust		P04035 HD	PRN
		P04040 J-K	Fixed
Patient ID	**Treatment arm**	P04048 B-C	Fixed
		P04055 T-W	PRN
P05092 cm	PRN	P04056 D-D	PRN
P05093 SAG	Fixed	P04059 M-H	Fixed
P05094 CAS	Fixed	P04060 K-J	PRN
P05095 DMB	PRN	P04066 K-E	Fixed
P05096 ML	Fixed	P04069 RES	PRN
P05097 MA	PRN	P04071 PDS	Fixed
P05098 LW	Fixed	P04072 JD	PRN
P05099 MAH	PRN	P04073 S-S	Fixed
		P04074 N-R	Fixed
		P04083 JRD	PRN
		P04086 DJS	Fixed

XI. Publication based on study

A Multicentre Prospective Open-label Randomized Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular edema.

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Abstract

OBJECTIVE:
To compare the clinical effectiveness and safety of 5-monthly fixed dosing versus pro-re-nata (PRN) Ozurdex treatment in patients with refractory diabetic macular edema (DME).
DESIGN:
Prospective, multicenter, randomized active-controlled non-inferiority clinical trial.
SETTING:
Medical Retina Clinics in 5 UK National Health Service hospitals.
PARTICIPANTS:
100 patients who attended Medical Retina Clinics for management of centre involving refractory DME.
INTERVENTIONS:
Participants were randomized 1:1 to either 5-monthly fixed dosing or optical coherence tomography (OCT) - guided PRN regimen of Ozurdex therapy for DME. Data were collected on best-corrected visual acuity (BCVA), patient reported outcome measures (PROM), macular thickness and morphology, diabetic retinopathy status, number of injections and adverse events from baseline for a period of 12 months.
MAIN OUTCOME MEASURES:
The primary outcome was the difference between arms in change in BCVA from baseline to 12 months. The pre-specified non-inferiority margin was 5 ETDRS letters. Key secondary outcomes included change in PROM scores; change in macular thickness; change in retinopathy and macular morphology and safety profile.
RESULTS:
The mean change in BCVA was +1.48 (SD 14.8) in the fixed arm versus -0.17 (SD 13.1) in the PRN arm, with adjusted effect estimate +0.97, 90% confidence interval (-4.01, +5.95), p=0.02 (per protocol analysis) and the conclusions of the ITT analysis were primarily supportive, -0.34 (-5.49, 4.81) p=0.07, but sensitive to an alternative assumption on missing data +0.28
(-4.72, 5.27) p = 0.04.
CONCLUSIONS:
The mean change in BCVA with five monthly fixed dosing of Ozurdex was non-inferior to OCT guided PRN Ozurdex therapy for refractory DME based on a per protocol analysis.

TRIAL REGISTRATION: Clinicaltrials.gov registry NCT01892163

INTRODUCTION

Centre-involving diabetic macular edema (DME) is a leading cause of moderate visual loss in diabetes.[1] The visual outcome and vision related quality of life of people with centre-involving DME have significantly improved with the initiation of inhibitors of vascular endothelial growth factor (VEGF).[2, 3] However, many patients still need frequent and multiple injections of anti-VEGF and up to 50% of treated patients do not achieve long term resolution of DME.[4, 5] Therefore, there is a significant unmet need for alternative interventions for refractory DME.[6]

Intravitreal steroids were the first class of intravitreal drugs that were evaluated for the treatment of this condition and remain a promising treatment modality for people with DME due to both its anti-inflammatory and anti-vascular permeability effects.[7,8] The Ozurdex (Allergan Inc.) drug delivery system is a sustained-release formulation for posterior-segment delivery of 700 micrograms dexamethasone. The Phase 3 MEAD study that evaluated the role of 6 monthly pro-re-nata (PRN) dosing of Ozurdex for DME reported that 22% of patients improved ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at the end of 3 years.[9] Another trial that compared the combination of Ozurdex and laser therapy versus laser therapy (PLACID) in DME reported that when Ozurdex was given at baseline and then optionally at month 6 or 9, the proportion of subjects with a 10 letter gain at all time points up to 12 months was significantly higher in laser treatment only. However, the study also reported that to obtain a sustained effect of Ozurdex, the treatment should be repeated at shorter intervals than every 6 months based on the changes observed in macular thickness on optical coherence tomography (OCT) and visual acuity.[10] The OCTOME study reported that the maximum treatment response of the drug occurred at 12 weeks before the effect wore off gradually. Therefore, a more frequent dosing between 16 and 20 weeks may be necessary to avoid the undulating effects on macular thickness and visual acuity.[11] A 16 weekly PRN dosing evaluated in the BEVORDEX study reported that 41% of the patients in the study improved 10 or more letters.[12] However, the OZLASE study reported that mandated Ozurdex injections at baseline and 16 weeks followed by PRN dosing based on stringent re-treatment criteria resulted in dose-dependent cataract formation or progression that confounded the potential for visual benefit (in press). Therefore, a great deal of uncertainty still exists on the optimal dosing of Ozurdex to adopt for patients with DME.

The objective of this study was to find the best dosing schedule that would provide optimal visual benefit with minimal burden on patients and hospital services. Therefore, we compared the risk-benefit ratio of 5-monthly fixed dosing versus OCT guided PRN dosing of Ozurdex in centre-involving refractory DME whilst keeping the treatment burden to a minimum. The primary objective was to evaluate whether 5-monthly fixed dosing of 700 µg Ozurdex is non-inferior to OCT- guided PRN dosing in patients with DME. Our null hypothesis was that the change in best corrected visual acuity (BCVA) between baseline and 12 months is more than 5 ETDRS letters lower in the fixed dosing (investigative) arm than in the OCT guided PRN dosing (standard) arm, to be assessed after adjusting for baseline BCVA and study site. The alternative hypothesis is that fixed dosing is non-inferior to OCT guided PRN dosing in terms of the change in BCVA between baseline and 12 months, being no lower in the fixed dosing arm than the PRN dosing arm by a non-inferiority margin of 5 ETDRS letters.

METHODS

Study design

This is a multicentre, prospective, randomized, active-controlled, non-inferiority study conducted across 5 sites in the United Kingdom (UK). The study was registered at www.clinicaltrials.gov/NCT01892163. The study protocol was approved by the UK Collaborative Research Ethics Committee (12/LO/1534). The principles of Good Clinical Practice were adhered throughout in accordance with the Declaration of Helsinki.

Study Population

Eligible patients were at least 18 years old with type 1 or type 2 diabetes. The key eligibility criteria for the study eye included: (1) best-corrected ETDRS visual acuity letter score 73 to 34 (20/40–20/200), (2) definite retinal thickening due to DME on clinical examination involving the centre of the macula assessed to be the main cause of visual loss, and (3) retinal thickness measured on spectral domain OCT >300 μm in the central subfield (CST) despite treatment. Principal exclusion criteria included: (1) macular ischaemia defined as angiographic evidence of foveal avascular zone of > 1000µm in diameter or presence of severe perifoveal intercapillary loss, (2) previous treatment for DME with intravitreal or peribulbar steroids in the last 6 months; anti-VEGF therapy in the last one month or macular laser within the prior 3 months, (3) active proliferative diabetic retinopathy requiring treatment at screening, (4) substantial cataract that, in the opinion of the investigator, was likely to be decreasing visual acuity by 3 lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if the eye was otherwise normal), (5) vitrectomised eye, (6) a diagnosis of glaucoma which in the opinion of a glaucoma specialist was at high risk of progression or ocular hypertension requiring at least one topical medication and (7) coexistent disease affecting the visual acuity of the study eye.

One eye was selected and treated as the study eye. If both eyes were eligible, the eye with the better visual acuity at screening was selected for treatment, unless, the patient preferred otherwise.

Interventions

All patients received baseline Ozurdex injection. Intravitreal Ozurdex injections were performed under local anaesthesia and post-injection topical antibiotics were used. Further Ozurdex injections in each arm were performed according to protocol-defined retreatment criteria. In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points. In the standard arm, participants were seen at baseline, 4 months and then monthly to assess the need for re-treatment. If the participants in standard arm were re-treated at any point, the next visit was after 4 months. In addition, safety visits were done at 1 and 8 weeks after any Ozurdex injection in either treatment arms. If there was any safety concern in the opinion of the investigator, more frequent optional post-injection assessment visits were allowed.

Re-treatment with Ozurdex was indicated if the CST on OCT exceeded 300 µm and

the intraocular pressure (IOP) was ≤ 25 mmHg. If the IOP was between 26 and 30mmHg, topical anti-glaucoma eye drops were given before treatment with Ozurdex at the same sitting. If the IOP recorded was 30 mmHg or more, anti-glaucoma eye drops were given and the patient was reviewed a week later and Ozurdex was injected only if the IOP had reduced to less than 30mmHg. Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation. The total duration of study participation was 12 months.

Randomization and treatment allocation

The study patients were randomized using a 1:1 allocation ratio into either the fixed dosing or the PRN dosing schedule of Ozurdex therapy via a bespoke web based randomization system hosted at the King's Clinical Trials Unit using the randomization sequence generation of block randomization with randomly varying block sizes, The use of concealed randomly varying block sizes ensured that treatment allocation did not become predictably determined towards the end of each block and thus protected pre-randomization allocation concealment.

Masking

The primary outcome assessors (optometrists and OCT technicians) at each site were masked to treatment allocation. The clinicians who administered the study treatment and those who performed the safety evaluations were not masked to the treatment arms.

Efficacy and Safety Assessments

We assessed BCVA using ETDRS charts at a starting distance of 4 meters. The PROM was assessed using the vision-specific National Eye Institute Visual Function Questionnaire (NEI VFQ-25)[13] and the validated diabetic retinopathy specific questionnaire (RetDQoL)[14] administered by staff at each site at baseline and 12 months. In addition, all patients completed a treatment satisfaction questionnaire (RetTSQ)[15] at baseline and at 12 months.

The OCT examinations were performed at every study visit using spectral domain OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). The posterior pole volume scan was performed over 20 degrees centred on the fovea, with 49 raster lines, separated by 120µm and ART of 24. The CST was obtained directly from the ETDRS map on the OCT. The site investigators also recorded the OCT morphological parameters using a standardized pre-defined protocol. Autofluorescence of the macula was performed on the Spectralis. The total area of hyper and hypoautofluorescence were measured using the in-built measuring tool. Fluorescein angiography was performed at baseline and month 12. In addition, red-free and 4-field color photographic images of the retina of the study eye were performed before fluorescein angiography at baseline and 12 months.

Safety Assessments

Safety was assessed by the 12-month incidence of adverse events (AEs) and serious AEs (SAEs), by ophthalmic examinations and IOP measurements over the 12-month assessment period. IOP was measured at each visit. The presence and severity of nuclear, cortical and posterior subcapsular lens opacities were measured during slit lamp examination using standardized photographs and the Lens Opacities Classification System II (LOCS II).[16] Systemic blood pressure and glycated haemoglobin (HbA1C) levels were also measured at baseline and 12 months.

Concomitant procedures

All medication(s)/treatment(s) except intravitreal anti-VEGF, periocular and intravitreal steroids and macular laser treatment were permitted during the trial period in the study eye of the patients. IOP lowering agents or surgery were allowed and consultations with a glaucoma specialist were permitted. Cataract surgery for visually significant cataract during the study period was at the discretion of the investigator. A masked grader determined whether the cataract was visually significant before planned cataract surgery. Steroid and antibiotic eye drops pre-and post-cataract surgery was permitted. Intraocular steroids, laser and anti-VEGF agents were allowed in the non-study eye. Pan retinal photocoagulation for retinal neovascularisation in both the study and non-study eye were also permitted.

Outcome measures

The primary outcome was assessed as the difference between arms in the mean change in BCVA between baseline and 12 months. Secondary outcomes included the proportion of patients with a gain or loss in visual acuity of ≥10 and ≥15 letters, distribution of BCVA change between arms in categories of ≥5 and <15 letters improvement and worsening and ≥ - 4 and $\leq$ 4 letters (i.e. no change), differences between arms in patient related outcome scores, the number of injections, the change in central subfield thickness and morphological characteristics of the macula on OCT, autofluorescence, the change in grading of diabetic retinopathy and the greatest diameter of the foveal avascular zone on fluorescein angiography and adverse events.

Sample size

This study was designed as a non-inferiority trial with the non-inferiority limit for the difference between study arms in the mean change in visual acuity at 12 months of 5 ETDRS letters lower under fixed dosing, assessed after adjusting for baseline BCVA ETDRS letter score and study site. If there is no statistically significant difference in the change in BCVA ETDRS letter score between baseline and 12 months, in the populations represented by two study arms, a sample size of 90 patients was required to be 83% certain that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) would be above the non-inferiority limit of 5 letters, assuming that the common standard deviation (SD) was 9 letters. The SD is based on the results of the Ranibizumab (RESOLVE) study.[17] The non-inferiority margin of 5 ETDRS letters is based on the CATT study (in which it is recognised as a commonly accepted margin)[18] and the results of the PLACID

study.[10] Allowing for 10% missing data, 100 patients were randomized (i.e. 50 patients per study arm).

Statistical Analysis

For the non-inferiority analysis of the primary outcome the following two populations were predefined: Intention to treat (ITT: all patients randomized) and per protocol (PP: those who met with the eligibility criteria and received the randomized treatment in accordance with the protocol). Corresponding ITT and PP 'available case' sample populations were pre-defined as those cases with available primary outcome data. Three patients did not provide primary outcome data at 12 months, one in the fixed arm and two in the PRN arm. This was less than the proportion anticipated to be lost to follow up (10%) confirming the pre-defined available case analysis approach to provide valid treatment effect estimates. At the request of the Data Monitoring Committee (DMC), an additional post hoc sensitivity analysis with alternative missing data assumptions was then conducted for the ITT population. This used in place of available case analysis, a last observation carried forward (LOCF) analysis approach, which carried forward data in these three patients who did not provide primary outcome data at 12 months.

The following significance levels were pre-defined. The primary outcome analysis used a one-sided p-value of 0.05, with a one-sided 95% confidence interval (or equivalently a two-sided 90% confidence interval), in accordance with a non-inferiority design. All other statistical tests used a two-sided p-value of 0.05, with a two-sided 95% confidence interval.

Summary measures for the baseline characteristics of each arm are presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Treatment effect estimates are reported as differences in means for continuous (approximate) normal data, differences in medians for non-normally distributed data and as odds ratios (using logistic regression) for binary data, after adjusting for baseline BCVA, study site and the respective baseline covariate, where available. Effect estimates are presented with a two-sided 95% confidence interval.

A pre-defined sensitivity analysis was conducted to assess the effect of having cataract surgery during the study on the primary outcome. This was restricted to those included in the primary analysis and was done by replacing the final visual acuity measurement with the last available visual acuity measurement before surgery and repeating the primary analysis.

A related within subgroup analysis of the primary outcome was performed on patients who were pseudophakic at baseline. This provided an unbiased but less precise estimate of the treatment effect in this subgroup which is free from any cataract-related issues. Secondary outcomes were analysed using ITT analysis to compare arms.

Except for the post hoc ITT using LOCF, all analyses were pre-specified and detailed in a Statistical Analysis Plan approved prior to data lock and therefore prior to any analyses and treatment allocation unmasking. All statistical analyses were conducted using Stata/IC (version 13.1, Stata Corp, College Station, Texas, USA).

RESULTS

A total of 100 patients were enrolled from February 2013 to November 2014 and randomized to study treatment across 5 sites. Figure 1 shows the CONSORTdiagram that describes the flow of participants at each stage. All recruited patients received the baseline Ozurdex injection and 49/50 (98%) in the fixed arm and 48/50 (96%) in the PRN arm completed the study providing primary outcome data (ITT). For the per protocol primary analysis, 2/50 (4%) patients and 3/50 (6%) patients were excluded from fixed and PRN arm respectively due to protocol deviations. The 3 patients excluded in the ITT were also excluded in the PP analysis. Tables 1 and 2 show that the treatment arms were similar at baseline with respect to demographic and study eye characteristics. The baseline mean BCVA in study eyes was 57.5 (SD 9.5) ETDRS letters in the fixed arm and 61.2 (SD 8.6) ETDRS letters in the PRN arm.

Primary outcome

Table 3 shows the ITT analysis (available cases i.e. all patients with at least one exposure to Ozurdex apart from the three without follow-up data at 12 months), the PP analysis and the post-hoc ITT analysis using LOCF of the primary outcome.

The ITT analysis effect estimate was -0.34 (-5.49, 4.81). Whilst this available case analysis interval overlapped the non-inferiority margin by half a letter, this was not seen in either PP analysis or the post-hoc ITT sensitivity analysis based on LOCF. For the ITT (available case), the mean improvement in the visual-acuity letter score in the fixed arm was 0.53 letters and 0 in the PRN arm. Both the PP analysis effect estimate of 0.97, 90% CI (-4.01, 5.95) and the post hoc ITT sensitivity analysis effect estimate of 0.28, 90% CI (-4.72, 5.27) support the claim of non-inferiority between treatment regimens.
Figure 2 summarizes the primary analyses results where the dashed vertical line represents the pre-specified non-inferiority margin.

Secondary outcomes

The proportion of eyes with a change in the letter score of 5, 10 or 15 are provided in Table 4. The proportion of patients in the fixed arm and PRN arm with ≥15 letters gain were 14% and 8% respectively whilst those who gained 10 or more letters comprised 24% in the fixed arm and 23% in the PRN arm. More patients (43%) gained 5 or more letters in the fixed arm compared to 33% in the PRN arm, however this was not statistically significant. The proportion of patients losing at least15 letters was also greater in the fixed arm (14%) compared to 8% in the PRN arm, albeit not statistically significantly. However, if we consider visual loss as ≥5 letters, both arms showed very similar outcomes of 22% and 23%.

The change at 12 months from baseline in composite score of patient related outcomes such as NEI-VFQ 25 was higher in the fixed arm than in PRN treatment effect estimate 3.1, 95% CI (-2.1, 8.3) although this was not statistically significant. Similarly RetTSQ composite score was higher in the fixed dosing than in the PRN –

treatment effect estimate 2.7 95% CI (-2.3, 7.7)- also not statistically significant.

The mean final macular thickness at 12 months was < 300µm (292.9µm) in the fixed arm compared to 372.3µm in the PRN arm. The mean reduction at 12 months from baseline of macular thickness was greater in the fixed arm compared to the PRN arm (-179.9µm vs -90.1µm) with a treatment effect estimate -71.3, 95% CI (-117.3, -25.3) indicating significantly higher reduction in the fixed arm. It is important to note however that this might reflect the difference in timings of injections between the two treatment arms - 45 of the fixed arm patients had treatments at or after 10 months compared with just 6 of the PRN patients). A detailed analysis of the OCT morphological parameters including autofluorescence will be reported subsequently. There were almost 50% more patients with hard exudates in the central 6mm retina in the PRN dosing than in the fixed dosing. The mean number of Ozurdex injections by 12 months was 2.86 in the fixed arm and 2.60 in the PRN arm despite the fact that the fixed arm received 5 monthly dosing whilst the PRN dosing was OCT-guided. The diabetic retinopathy status at 12 months was similar between the dosing arms.

As a final sensitivity analysis, a within subgroup analysis of the primary outcome was also performed on patients who were pseudophakic at baseline. The baseline visual acuity of the pseudophakic group was 58.6 in the fixed arm and 61.3 in the PRN arm. The final mean visual acuities of the pseudophakic group in the fixed arm and PRN were 58.3 and 63.2 respectively. Non-inferiority was only observed in the per protocol sensitivity analysis however the numbers were small (15 vs. 10 pseudophakic patients in the fixed and PRN arm respectively) and as such no firm inferences can be drawn.

Safety outcomes

The proportion of patients that developed with IOP>30mmHg were 20% in the fixed arm and 34% in the PRN arm. Sixty four percent (18/28) patients initiated on topical IOP lowering medication continued on the medication until end of the study and 3 patients required more than 1 topical medication. No patients required surgical intervention for raised IOP in either arm. The topical medications were either initiated at the 8-week visit following a Ozurdex injection or at the next re-treatment visit.

Out of a total of 34 phakic patients in the fixed arm, 27 (79%) showed showed new onset or progression of cataract based on change in the LOC II grading by at least 1 grade at final visit. These included 3 nuclear, 3 cortical, 8 PSCO and 12 mixed cataract and 1 had cataract surgery. In the PRN arm with 39 phakic patients, 30 (77%) patients showed progression and included 3 nuclear,6 cortical, 6 PSCO and 11 mixed cataract and 4 had cataract surgery. There was 1 case of retinal detachment in the PRN arm and 1 case of endophthalmitis in the fixed arm and both events were reported as related to the intervention.

The change in greatest linear dimension and area of foveal vascular zone from baseline to 12 months were not significantly different between arms. There was no difference between arms in changes in systolic and diastolic blood pressure and glycated haemoglobin.

DISCUSSION

The ITT (available case) analysis did not demonstrate non-inferiority. However, the per protocol and the post hoc ITT analysis supported non-inferiority, and it should be observed that the data were more variable than had been anticipated at the point of sample size computation. Trialists do not agree on whether a PP or ITT analysis should be carried out when examining non-inferiority. From a regulatory perspective both populations are of interest and our protocol clearly specified an examination of both. The European Medicines Agency publication states that a non-inferiority trial must show non-inferiority in both the ITT and the PP populations and advise close examination where there are discrepancies. It is for this reason that we conducted a post hoc sensitivity ITT analysis using LOCF for the three subjects who withdrew. This agreed with the PP population and further it should be noted that the original ITT analysis missed the margin by half a letter. In summary therefore we believe that this study lends support to the statement of non-inferiority, i.e. that the results of this trial show that there is no evidence that 5 monthly fixed dosing of Ozurdex is non-inferior to OCT-guided PRN regimen of Ozurdex in patients with refractory DME in terms of visual acuity at 12 months. Both arms showed similar visual acuity changes despite more frequent monitoring in the PRN arm. Likewise, both arms showed low mean change in visual acuity at 12 months from baseline despite significant reduction in the central macular thickness, more so in the fixed arm. This may be because cataract progression might have confounded the visual outcomes in both arms or the suggested reduction in macular thickness was transient.

The proportion of patients gaining and losing vision were also similar in the two arms. However, more patients (although not statistically significant) benefited from 5 or more letter gain in the fixed arm. The patient related outcomes were better with the fixed dosing in terms of vision related quality of life and patient satisfaction, although again, not statistically significant with these data. Better results may have been seen because the treatment regime was known to patients in the fixed arm but unknown to the patients until the day of the hospital appointment in the PRN arm. Anecdotal evidence is that patients report considerable distress when there is uncertainty about whether they will be given an injection or not.

About one in five patients also lost ≥5 letters with Ozurdex in both arms and this concurs with previous studies. In the BEVORDEX study, 11% lost 10 or more letters in the Ozurdex arm compared to none in the bevacizumab arm at 12 months. Most anti-VEGF trials report less than 5% of patients losing vision. This may be attributed mainly due to the development of cataract.

The ocular and systemic safety profiles of Ozurdex in both treatment groups of this study were very similar to previous reports with no unexpected events. Although cataract progression and IOP increases are expected complications of corticosteroid treatment, the incidence did not differ between treatment pathways in this study. The increases in IOP that occurred were typically manageable with topical medication. The timing of IOP rises was predictable, and the incidence and magnitude of IOP elevations did not increase upon repeated injection over 12 months probably because patients who were initiated on topical IOP lowering medications continued

on the medications until end of the study.

The results of this study suggest that patients need not be reviewed for IOP check at 1 week following ozurdex injection as no patients developed a rise in IOP at this time-point. In most patients who developed IOP rise, this was observed at the visit 8 weeks post injection. We therefore recommend a post-injection IOP check at about 4-8 weeks especially in eyes with established glaucoma or ocular hypertension or previous history of steroid induced ocular hypertension in both arms.

As previously shown, cataract progression is dose related and more frequent dosing than 6 monthly resulted in a higher proportion of cataract development and progression that affected final visual acuity gain. In the MEAD study, 6 monthly PRN Ozurdex resulted in reduced improvement in BCVA at 15 months from baseline after a mean of 2.3 injections in the first year. The OZLASE study showed that mandated Ozurdex at baseline and at 16 weeks followed by PRN regimen with a mean of 3.5 injections in 12 months resulted in 21/27 (78%) of eyes showing cataract progression that confounded final visual acuity (personal commnication). It should be noted that there is no standard definition of progression of cataract or for the threshold for cataract surgery. Differences in rate of cataract progression reported between studies using varying dosing regimens may not be related to the dosing regimen. We defined cataract progression as a 1-step change in LOC II score while the BEVORDEX study defined as a 2-step change in LOC II grading.

The MEAD study showed that 23.3% of pseudophakic eyes gained 15 or more letters at 3 year follow up compared to 22.2% in the whole study. Our study population also showed that 22% gained 15 or more letters in both arms together with no significant difference in visual outcome in pseudophakic eyes. We believe that intravitreal Ozurdex is very effective in causing resolution of macular fluid. However, unlike the earlier studies such as the MEAD study that included patients with persistent fluid post-laser treatment, recent studies include patients that have been refractory to laser therapy and anti-VEGF agents. Therefore, these are truly refractory cases and visual acuity is unlikely to improve in many of these cases despite complete resolution of macular edema.

If Ozurdex is planned as an alternate option for patients with refractory DME, this study suggests that 5-monthly fixed dosing is an effective approach and may be more acceptable to patients. Patients should be warned about cataract progression and that significant gains in visual acuity is less likely compared to anti-VEGF agents.

The strengths of this trial include secure randomisation, size, the multicentre design, low rates of losses to follow-up, and use of outcome measures appropriate to the primary outcome. Limitations of the study include the fact that the 12 month cut off of the study may have been more advantageous to the fixed arm than the PRN arm because all patients received mandated dosing in the fixed arm at 10 months and the maximal effect on vision and macular thickness is expected at 12 months while the injections flexibility in the PRN arm may have meant that not all patients would have attained maximal efficacy by 12 months. However, this did not alter the visual outcome between arms and may only explain the differences in central macular thickness between arms. The non-inferiority margin of 5 letters might be considered

large by some and hence a limitation of the study; however, this was selected based on previous studies that showed that a 5 letter change is required for patients to perceive a treatment benefit.[18]The sample size is a limitation of this study. Despite being powered based on equivalent studies, the results showed more variability in the outcome than was anticipated. Recruitment had completed prior to any outcome data being available so adjustment to the sample size during the study was not possible.

To our knowledge, this is the first large prospective, randomized controlled trial of dosing regimens with Ozurdex in DME. Several studies have compared Ozurdex to other interventions including sham but comparisons between Ozurdex arms in different trials are complicated due to different trial treatment regimen. Owing to the large study population and the strict adherence to accepted research methodology in this trial, the results provide concise data, suggesting that 5-monthly fixed dosing is non-inferior to PRN treatment both in terms of visual outcome and safety profile.

Conclusions and policy implications

We have provided useful information for clinicians using Ozurdex to treat DME in patients refractory to laser and or anti-VEGF. Although the visual outcomes are not as effective as those reported with anti-VEGF agents in DME at one year, if Ozurdex is used, this study suggests that the fixed dosing arm is an alternative treatment regimen for DME that is as effective as PRN dosing and still has a profound drying effect of the macula.

In summary, this study shows that 5-monthly fixed dosing of Ozurdex is non-inferior to OCT-guided PRN dosing in patients with DME with a similar safety profile and better feasibility and acceptability. The relative advantages and disadvantages of these treatment regimens should be discussed with DME patients so that an informed decision can be made.

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Chair of TSC: Sheena Koshy FRCOphth
DMC members: Jignesh Patel, FRCOphth, Niaz Islam, FRCOphth, Irene Stratton MSc.

Figure 1: CONSORT flow diagram

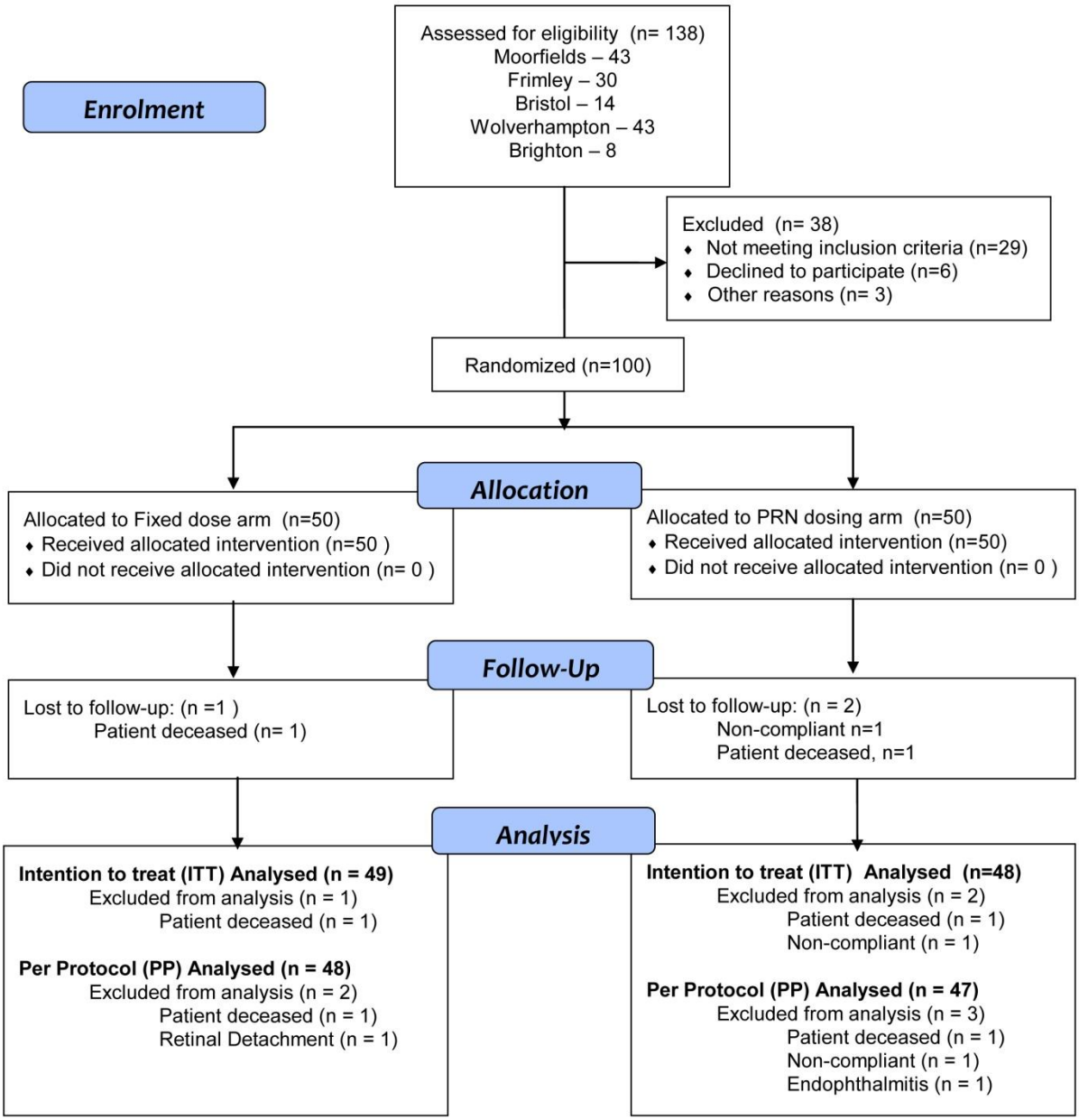

Figure 2:

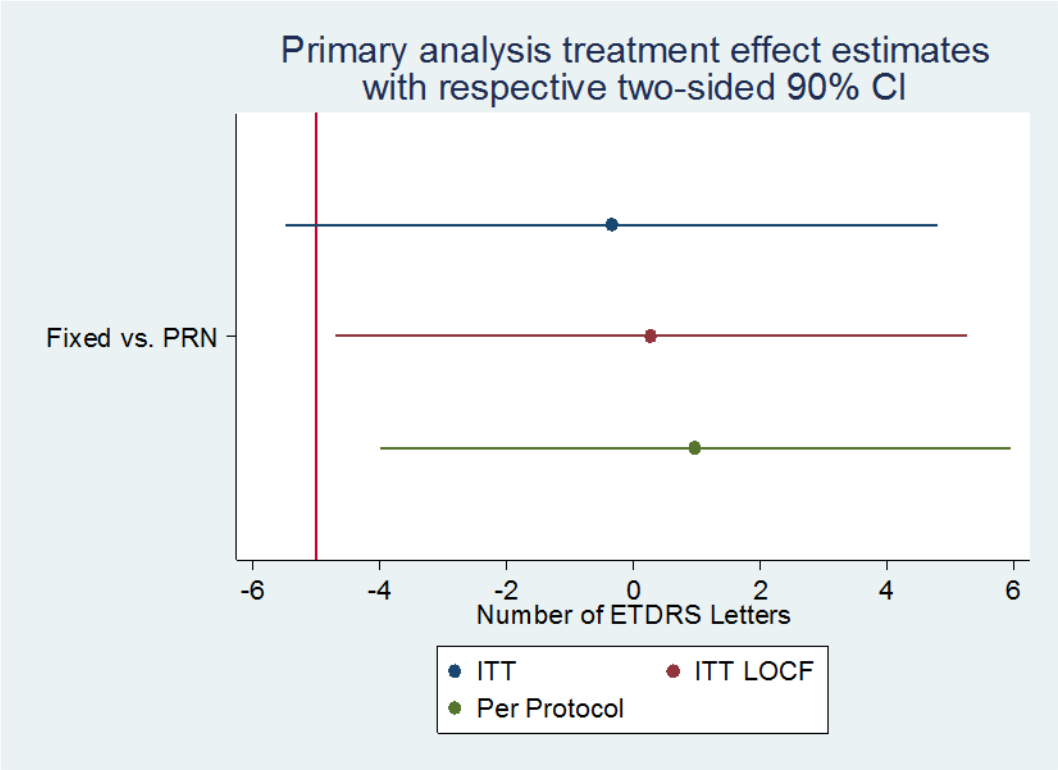
Primary analysis treatment effect estimates
with respective two-sided 90% CI
Fixed vs. PRN
-6
-4
-2
0
2
4
6
Number of ETDRS Letters
ITT
ITT LOCF
Per Protocol

Table 1: Non-Ocular Baseline Characteristics by Study Arm

	Fixed dosing	PRN dosing
Males, n (%) [N]	40 (80) [50]	34 (68) [50]
Age (years), mean (SD) [N]	63.8 (11.1) [50]	65.4 (9.8) [50]
Ethnicity [N]	[50]	[50]
White / Caucasian, n (%)	34 (68)	35 (70)
Black or African, n (%)	5 (10)	5 (10)
South Asian, n (%)	10 (20)	8 (16)
Other, n (%)	1 (2)	2 (4)
Diabetes [N]	[50]	[50]
Type 1, n (%)	7(14)	2 (4)
Type 2 on insulin, n (%)	22 (44)	22 (44)
Type 2 on tablets, n (%)	21 (42)	26 (52)
Duration of Diabetes (months) median (IQR) [N]	192 (112, 255) [50]	196 (124, 249) [50]
HbA1c (%), mean (SD) [N]	8.1 (1.4) [50]	7.7 (1.3) [50]
Systolic BP (mmHg), mean (SD) [N]	148.5 (20.5) [50]	142.8 (20.5) [50]
Diastolic BP (mmHg), mean (SD) [N]	79.3 (9.8) [50]	77.7 (10.8) [50]

PRN= pro-re-nata; n = number of patients; N = total number of patients; SD = standard deviation; IQR = interquartile range; BP = blood pressure; HbA1c = glycated hemoglobin

Table 2: Ocular Baseline Characteristics by Study Arm

	Fixed dosing	PRN dosing
ETDRS BCVA, mean (SD) [N]	57.5 (9.5) [50]	61.2 (8.6) [50]
Duration of DME (months), median (IQR) [N]	35.5 (15.0, 51.0) [50]	37.0 (18.0, 48.0) [50]
Prior treatments		
Macular laser therapy, n (%) [N]	46 (92) [50]	48 (96) [50]
Pan-retinal photocoagulation, n (%) [N]	14 (28) [50]	8 (16) [50]
Intravitreal Anti-VEGF, n (%) [N]	17 (34) [50]	17 (34) [50]
Intravitreal steroids, n (%) [N]	5 (10) [50]	3 (6) [50]
OCT findings		
CRT (µm), mean (SD) [N]	479.8 (128.4) [50]	466.7 (144.1) [50]
CST (µm), mean (SD) [N]	472.4 (113.5) [50]	467.9 (126.4) [50]
Macular volume (mm^3), mean (SD) [N]	10.0 (2.5) [50]	10.4 (2.1) [50]
Lens status		
Pseudophakic, n (%) [N]	16 (32) [50]	11 (22) [50]
Phakic, n (%) [N]	34 (68) [50]	39 (78) [50]
Presence of cataract, n (%) [N]	24 (70.6) [34]	31 (79.5) [39]
ETDRS grade of retinopathy		
Mild NPDR, n (%) [N]	16 (32) [50]	17 (34) [50]
Moderate NPDR, n (%) [N]	17 (34) [50]	21 (42) [50]
Severe NPDR, n (%) [N]	5 (10) [50]	7 (14) [50]
Treated PDR, n (%) [N]	11 (22) [50]	5 (10) [50]
Not available, n (%) [N]	1 (2) [50]	0 (0) [50]
FFA findings		
FAZ GLD (mm), mean (SD) [N]	808.5 (271.8) [50]	769.0 (190.4) [50]
FAZ Area (mm^2), median (IQR) [N]	0.5 (0.3, 0.7) [49]	0.4 (0.3, 0.6) [50]

PRN= pro-re-nata; n = number of patients; N = total number of patients; SD = standard deviation; IQR = interquartile range; ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; DME= diabetic macular edema; CRT = central retinal thickness; CST = central subfield thickness; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; FAZ = foveal avascular zone; GLD = greatest linear dimension; FFA = Fundus fluorescein angiography; VEGF = Vascular endothelial growth factor

Table 3: Primary Analyses by Study Arm – Efficacy outcome measures

	Fixed dosing ETDRS BCVA, mean (SD) [N]	PRN dosing ETDRS BCVA, mean (SD) [N]	Effect Estimate (two-sided 90% CI)	One-sided P-value
Intention To Treat (ITT) Analysis (available case)				
At 12 months	57.8 (18.5) [49]	61.4 (14.0) [48]	-	-
Change from Baseline*	0.53 (16.1) [49]	0 (13.0) [48]	-0.34 (-5.49, 4.81)	0.07
Per Protocol (PP) Analysis				
At 12 months	58.5 (17.9) [48]	61.1 (14.0) [47]	-	-
Change from Baseline*	1.48 (14.8) [48]	-0.17 (13.1) [47]	0.97 (-4.01, 5.95)	0.02
Post Hoc Last Observation Carried Forward (LOCF) ITT Analysis				
At 12 months	58.0 (18.4) [50]	60.8 (14.2) [50]	-	-
Change from Baseline*	0.52 (15.9) [50]	-0.44 (13.0) [50]	0.28 (-4.72, 5.27)	0.04

ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; N = total number of patients; CI = Confidence interval; PRN = pro-re-nata

* Adjusted for baseline BCVA and study site

Table 4: Secondary Analyses by Study Arm – Efficacy outcome measures at 12 months from baseline*

		Fixed dosing	PRN dosing	
BCVA (ETDRS letters)		**No of patients, n (%) [N]**	**No of patients, n (%) [N]**	**Odds Ratio**
Improvement	≥ 10 letters	12 (24) [49]	11 (23) [48]	0.82 (0.3, 2.3)
	≥ 15 letters	7 (14) [49]	4 (8) [48]	1.3 (0.33, 5.40)
	≥ 5 and < 15 letters	14 (29) [49]	12 (25) [48]	1.3 (0.50, 3.36)
Stabilization	< 15 letters loss	42 (86) [49]	44 (92) [48]	0.56 (0.15, 2.18)
No Change	≥ -4 and ≤ 4 letters	17 (35) [49]	21 (44) [48]	0.7 (0.3, 1.7)
Worsening	≥ 5 and < 15 letters	4 (8) [49]	7 (15) [48]	0.65 (0.17, 2.60)
	≥ 15 letters	7 (14) [49]	4 (8) [48]	1.76 (0.46, 6.76)
ETDRS grade of retinopathy		**No of patients, n (%) [N]**	**No of patients, n (%) [N]**	**Odds Ratio**
	Mild NPDR	13 (28) [47]	18 (40) [45]	-
	Moderate NPDR	16 (34) [47]	16 (36) [45]	-
	Severe NPDR	6 (13) [47]	4 (9) [45]	-
	Treated PDR	12 (25) [47]	7 (15) [45]	-
PROM - composite score change		**Mean (SD) [N]**	**Mean (SD) [N]**	**Effect Estimate (95% CI)**
	NEI-VFQ-25	3.02 (15.4) [49]	-0.45 (12.2) [47]	3.1 (-2.1, 8.3)
	RetDQoL	-0.38 (1.7) [49]	-0.14 (1.6) [48]	-0.16 (-0.8, 0.5)
	RetTSQ	4.4 (12.7) [49]	3.6 (15.1) [47]	2.7 (-2.3, 7.7)
Central Subfield Thickness		**Mean (SD) [N]**	**Mean (SD) [N]**	**Effect Estimate (95% CI)**
	At 12 months	292.9 (118.9) [47]	372.3 (117.3) [47]	-
	Change from Baseline	-179.9 (172.4) [47]	-90.1 (96.2) [47]	-71.34 (-117.33, -25.34)
Treatment		**Mean (SD) / Median (IQR) [N]**	**Mean (SD) / Median (IQR) [N]**	**Effect Estimate (95% CI)**
	No of injections per patient	2.86 (0.45) / 3 (3, 3) [50]	2.60 (0.70) / 3 (2, 3) [50]	0.26 (0.03, 0.49)

PRN= pro-re-nata; ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; n= number of patients; N = total number of patients; IQR= Interquartile range; CI= Confidence Interval; NPDR= Non-proliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy; PROM= Patient Related Outcome Measures; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire; RetDQoL = Retinopathy Dependent Quality of Life questionnaire; RetTSQ = Retinopathy Treatment Satisfaction Questionnaire

* Adjusted for baseline BCVA and study site

Table 5: Sensitivity analysis to assess the effect of baseline lens status and cataract surgery during the study

	Fixed dosing ETDRS BCVA, mean (SD) [N]	PRN dosing ETDRS BCVA, mean (SD) [N]	Effect estimate (Two-sided 90% CI)	One-sided P-value
ITT Sensitivity Analysis (available case): Cataract Surgery				
At 12 months	57.6 (18.6) [49]	59.8 (14.1) [48]	-	-
Change from Baseline	0.35 (16.0) [49]	-1.65 (13.2) [48]	1.18 (-3.97, 6.34)	0.02
ITT Sensitivity Analysis (available case): Pseudophakic at Baseline				
At 12 months	58.3 (19.9) [15]	63.2 (14.5) [10]	-	-
Change from Baseline	0.53 (14.7) [15]	1.2 (13.6) [10]	0.73 (-11.4, 12.9)	0.2
PP Sensitivity Analysis: Cataract Surgery				
At 12 months	58.3 (18.0) [48]	59.4 (14.0) [47]	-	-
Change from Baseline	1.29 (14.7) [48]	-1.85 (13.2) [47]	2.51 (-2.48, 7.50)	0.007
PP Sensitivity Analysis: Pseudophakic at Baseline				
At 12 months	61 (17.7) [14]	63.2 (14.5) [10]	-	-
Change from Baseline	3.78 (7.8) [14]	1.2 (13.6) [10]	5.81 (-2.44,14.05)	0.02
Post Hoc LOCF ITT Sensitivity Analysis: Cataract Surgery				
At 12 months	57.8 (18.5) [50]	59.2 (14.2) [50]	-	-
Change from Baseline	0.34 (15.8) [50]	-2.02 (13.1) [50]	1.73 (-3.26, 6.72)	0.01
Post Hoc LOCF ITT Sensitivity Analysis: Pseudophakic at Baseline				
At 12 months	59.1 (19.5) [16]	61.9 (14.4) [11]	-	-
Change from Baseline	0.5 (14.2) [16]	0.64 (13.1) [11]	1.22 (-9.51,11.96)	0.16

ETDRS = Early Treatment Diabetic Retinopathy Study; BCVA = best corrected visual acuity; SD = standard deviation; CI= Confidence Interval; PRN = pro-re-nata; N = total number of patients; LOCF= Last Observation Carried Forward; PP= Per Protocol; ITT= Intention To Treat; PP = per protocol

Table 6: Adverse and serious adverse events

	Fixed	PRN
Total adverse events (n)	**167**	**158**
Ocular adverse events	**136**	**123**
Subconjunctival haemorrhage	83	57
Raised IOP in study eye	8	13
Vitreous haemorrhage	3	3
Cataract progression	5	7
Others	37	43
Non-ocular Adverse Events	**31**	**35**
Total Serious Adverse Events (n)	**9**	**10**
Ocular Serious Adverse Events	**3**	**6**
Retinal detachment	1	0
Cataract surgery in study eye	1	4
Endophthalmitis	0	1
Others	1	1
Non-ocular Serious Adverse Events	**6**	**4**
Death	1	1
Others	5	3

n= total number of events; PRN = pro-re-nata; IOP = intraocular pressure