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

Summary

EudraCT number	2012-003661-17
Trial protocol	GB
Global end of trial date	10 November 2014

Results information

Result version number	v1 (current)
This version publication date	23 August 2018
First version publication date	23 August 2018
Summary attachment (see zip file)	Study Summary (OZDRY study report final.pdf) Trial Results (SIVS1007_Final_Analysis.pdf)

Trial information

Trial identification

Sponsor protocol code	Protocol SS01 Version 7.0 dated 07-

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01892163
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Moorfields Eye Hospital
Sponsor organisation address	162 City Road, London, United Kingdom, EC1V 2PD
Public contact	Prof. Sobha Sivaprasad, Moorfields Eye Hospital, sobha.sivaprasad@moorfields.nhs.uk
Scientific contact	Prof. Sobha Sivaprasad, Moorfields Eye Hospital, sobha.sivaprasad@moorfields.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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).

Protection of trial subjects:

AE and SAE were reported at any point in the study. All AEs and SAEs were discussed at the DMC. The DMC reviewed the accruing trial data and on-going safety issues. There were no safety issues, but if there were any issues that needed further action, these would have been escalated to the Trial Steering Committee who would have then decided whether the study continues, terminates or if any substantial changes to the protocol were required.

There was a one week and 8 weeks visit after the baseline and all subsequent Ozurdex injections in both treatment arms. If there was any safety concern in the opinion of the investigator, patients were assessed at an optional post-injection assessment visit.

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.

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

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	05 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	45
From 65 to 84 years	53
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

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).

Pre-assignment

Screening details:

Eligible patients were at least 18 years old with diabetes, BCVA letter score 73 to 34, OCT >300 µm in the central subfield (CST) despite treatment. Exclusion was macular ischemia, previous treatment for DME with steroids in the last 6 months; anti-VEGF therapy in the last one month or macular laser in 3 months, active PDR and substantial cataract

Pre-assignment period milestones

Number of subjects started	138[1]
Number of subjects completed	100

Pre-assignment subject non-completion reasons

Reason: Number of subjects	not meeting inclusion criteria: 29
Reason: Number of subjects	declined to participate: 6
Reason: Number of subjects	not known: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 138 patients were screened, 100 patients were enrolled and completed, 38 patients were not enrolled.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[2]

Blinding implementation details:

Primary outcome assessors (optometrists and OCT technicians) were masked to treatment allocation. 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.

Arms

Are arms mutually exclusive?	Yes
Arm title	Fixed

Arm description:

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
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

Arm type	intervention arm

Investigational medicinal product name	700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)
Investigational medicinal product code	
Other name	OZURDEX
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

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.
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 addition, safety visits were done at 1 and 8 weeks after any Ozurdex injection in either treatment arms.

Arm title	PRN dosing arm

Arm description:

In the standard arm (PRN), 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.
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.

Arm type	standard
Investigational medicinal product name	700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)
Investigational medicinal product code	
Other name	OZURDEX
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

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.
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 addition, safety visits were done at 1 and 8 weeks after any Ozurdex injection in either treatment arms.

Investigational medicinal product name	700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)
Investigational medicinal product code	
Other name	Ozurdex
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

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:

Investigational medicinal product name	Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS)
Investigational medicinal product code	
Other name	Ozurdex
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

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

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The trial was single blinded (the optometrists and OCT technicians were blinded to treatment allocation. The patients and clinicians who administered the study treatment and those who performed the safety evaluations were not blinded to the treatment arms).

Number of subjects in period 1	Fixed	PRN dosing arm
Started	50	50
Completed	49	48
Not completed	1	2
death	1	1
non compliant	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Fixed

Reporting group description:

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
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

Reporting group title	PRN dosing arm

Reporting group description:

In the standard arm (PRN), 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.
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.

Reporting group values	Fixed	PRN dosing arm	Total
Number of subjects	50	50	100
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	63.8	65.4	
standard deviation	± 11.1	± 9.8	-
Gender categorical Units: Subjects			
Female	10	16	26
Male	40	34	74
Best Corrected Visual Acuity Units: ETDRS letters			
arithmetic mean	57.5	61.2	
standard deviation	± 9.5	± 8.6	-
OCT Central subfield thickness Units: microns			
arithmetic mean	472.4	467.9	
standard deviation	± 113.5	± 126.4	-

End points

End points reporting groups

Reporting group title	Fixed

Reporting group description:

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
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

Reporting group title	PRN dosing arm

Reporting group description:

In the standard arm (PRN), 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.
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.

Primary: BCVA at 12 months ITT analysis

End point title	BCVA at 12 months ITT analysis

End point description:

End point type	Primary

End point timeframe:

12 months

End point values	Fixed	PRN dosing arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: ETDRS letters				
arithmetic mean (standard deviation)	57.8 (± 18.5)	61.4 (± 14)		

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

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.

Comparison groups	Fixed v PRN dosing arm

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	descriptive
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard deviation

Secondary: Change in central retinal thickness on OCT at 12 months

End point title	Change in central retinal thickness on OCT at 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Fixed	PRN dosing arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: microns				
arithmetic mean (standard deviation)	-179.9 (± 172.4)	-90.1 (± 96.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: No of injections per patient

End point title	No of injections per patient

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Fixed	PRN dosing arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: number				
arithmetic mean (standard deviation)	2.86 (± 0.45)	2.6 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: February 2013 to November 2014	
Assessment type	Systematic

Dictionary used	
Dictionary name	not used dictionary
Dictionary version	0

Reporting groups	
Reporting group title	Fixed dose arm
Reporting group description: -	
Reporting group title	PRN dose arm
Reporting group description: -	

Serious adverse events	Fixed dose arm	PRN dose arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 50 (18.00%)	10 / 50 (20.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Others general			
subjects affected / exposed	5 / 50 (10.00%)	3 / 50 (6.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract surgery in study eye			

subjects affected / exposed	1 / 50 (2.00%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other ocular			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Fixed dose arm	PRN dose arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	50 / 50 (100.00%)	
General disorders and administration site conditions			
All Ocular			
subjects affected / exposed	50 / 50 (100.00%)	50 / 50 (100.00%)	
occurrences (all)	136	123	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

12 month cut off of the study favouring Fixed dose patients, as they had injections at 10 months - so better 12 month results, than PRN
Non-inferiority margin of 5 letters might be considered large by some
The sample size is a limitation

Notes: