Clinical trial results:
Macular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial

Summary

EudraCT number	2017-003243-37
Trial protocol	GB
Global end of trial date	02 February 2022

Results information

Result version number	v1 (current)
This version publication date	06 October 2023
First version publication date	06 October 2023

Trial information

Trial identification

Sponsor protocol code	140840

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02623426
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johns Hopkins Bloomberg School of Public Health
Sponsor organisation address	415 N. Washington Street, Baltimore, United States, 21231
Public contact	Nancy Prusakowski, MERIT Coordinating Center Johns Hopkins Bloomberg School of Public Health, 001 4109558164, nprusak1@jhu.edu
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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	31 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2021
Global end of trial reached?	Yes
Global end of trial date	02 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Macular oedema is swelling of the retina at the back of the eye. It can cause vision loss and is a common complication in patients who have the eye condition uveitis (inflammation inside the eye). The MERIT Trial was designed to compare three treatments for uveitic macular oedema, to find out which intravitreal therapy offers the best balance of effectiveness and tolerability in eyes with controlled uveitis but persistent macular edema, specifically by comparing the relative efficacy and safety of intravitreal ranibizumab (Lucentis®) and intravitreal methotrexate to intravitreal dexamethasone implant (Ozurdex®) for the treatment of persistent uveitic macular oedema.
The primary outcome will be the percent change in macular thickness from the baseline to the 12 week visit.

Protection of trial subjects:

The injection procedures and treatment algorithm are consistent with standard clinical treatment, e.g., sterile technique, prophylactic pressure lowering medicine instilled prior to procedure. To minimize risks associated with increased ocular pressure post-injection, patients with uncontrolled ocular hypertension or glaucomatous changes are excluded from the trial. Pregnancy testing are required for women of childbearing potential before intravitreal injections of methotrexate or ranibizumab. Adverse events encountered will be managed by the best medical judgment of the treating physician.

Confidentiality of patient data is maintained in accordance with legal regulations. Protected health information is kept in a secure place. Name, social security number, address, and other such personal data are kept solely at the clinical center where the patient receives her/his clinical care. Such information will not be transmitted to the Coordinating Center or to other study sites. A dataset limited so as to contain a minimal amount of protected health information–that required to make the data useful for accomplishing the purposes of the trial may be disclosed, as needed, to collaborating study sites, the NEI, and the FDA, as will be stated on a study privacy acknowledgment form signed by the participant at the time of enrollment.. This privacy acknowledgment will be designed to conform to specifications of HIPAA regulations, and any other relevant regulations, as approved by the local governing authorities invested with oversight of HIPAA regulations at each participating site. Clinically relevant information from the study may be placed in the patient's medical record. Release of protected health information to any other persons or organizations will require additional written consent of the patient affected, except as required by law.

Background therapy: -

Evidence for comparator:

Recent pilot studies have shown intravitreal methotrexate (MTX) and intravitreal ranibizumab (Lucentis®, Genentech Inc., San Francisco, CA) to be promising treatments for uveitic ME, and intravitreal dexamethasone implant (Ozurdex®, Allergan, Irvine, CA) has recently been approved for uveitic ME in patients with non-infectious uveitis. In addition to being effective, intravitreal MTX and ranibizumab potentially may have less ocular side effects than corticosteroids, particularly less IOP elevation

Actual start date of recruitment	01 May 2017
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: 25
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	India: 27
Country: Number of subjects enrolled	United States: 127
Worldwide total number of subjects	194
EEA total number of subjects	0

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)	132
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening details:
353 screened, 194 randomized
Excluded
Major reasons for exclusion were;
central subfield macular thickness within the normal range for the OCT machine (38%)
Patient preference (14%)
Uveitis (9%)
IOP issues (9%)

Period 1

Period 1 title	Overall trial 12 weeks (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Reading center graders assessing primary outcome and visual acuity examiners masked to treatment

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone intravitreal implant 0.7mg

Arm description:

Dexamethasone intravitreal implant 0.7mg.Eligible eye(s) treated at study visit M01 (week 0).
Retreatment required at study visit M03 (8 weeks) if re-treatment criteria met.
Standard preparation as described for intravitreal injections.
(Ozurdex®, Allergan, Irvine, CA)

Arm type	Active comparator
Investigational medicinal product name	Ozurdex (0.7 mg dexamethasone pellet)
Investigational medicinal product code	
Other name	intravitreal dexamethasone pellet, Ozurdex
Pharmaceutical forms	Emulsion for injection
Routes of administration	Intraocular use

Dosage and administration details:

• Prepare eye for injection using the following sequence of steps:
- Consider placing 2-3 drops of 5% povidone iodine in the lower fornix and/or using sterile cotton-tipped applicators soaked in 5% or 10% povidone iodine to swab the upper and lower eyelid margins and the upper and lower eyelashes (Optional)
- Retract the eyelids and lashes away from the injection site and needle for the duration of the procedure (use of an eyelid speculum is optional)
- Consider additional anesthesia with the application of one or two cotton-tipped applicators soaked in topical anesthetic over the intended injection site for at least 30 seconds. The use of lidocaine gel or other types of viscous anesthetic (e.g. TetraVisc™) is also permitted.
A subconjunctival anesthetic can be used in specific circumstances in which the study ophthalmologist believes that topical anesthetic is not sufficient to minimize discomfort
• Remove the lid speculum/unretract eyelid and lashes and avoid any excess pre

Arm title	Intravitreal methotrexate 400µg in 0.1mL

Arm description:

Drug: Intravitreal Methotrexate 400 µg
Intravitreal Methotrexate 400 µg injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to the injection.

Arm type	Active comparator
Investigational medicinal product name	Intravitreal methotrexate 400 µg in 0.1 mL
Investigational medicinal product code	
Other name	Intravitreal methotrexate 400 µg in 0.1 mL
Pharmaceutical forms	Emulsion for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal methotrexate 400 µg in 0.1 mL Eligible eye(s) treated M01+ Retreatment required at M02, M03 if retreatment criteria met Retreatment permitted at M04 and later if retreatment criteria met
Retreatment criteria:
1. Central subfield thickness greater than 1.1 times the upper limit of normal (330 µm for Zeiss and Topcon SD OCT and 352 µm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield.
1. IOP of <25 mm Hg (treatment with ≤3 IOP-lowering agents permitted), IOP criteria for initial injection of study treatment in eligible eye(s) is ≤21 mm Hg with ≤3 IOP-lowering agents

Arm title	Intravitreal ranibizumab 0.5mg in 0.05mL

Arm description:

Intravitreal Ranibizumab 0.5 mg injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to the injection.
(Lucentis®, Genentech Inc., San Francisco, CA)
Eligible eye(s) treated at study visit M01 (week 0).

Retreatment required at study visit M03 (8 weeks) if re-treatment criteria met.
Retreatment permitted at later time points if retreatment criteria met.
Re-treatment criteria:

Central subfield thickness greater than 1.1X upper limit of normal (330 µm for Zeiss and Topcon Spectral Domain (SD) Optical Coherence Tomography (OCT) and 352 µm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield.
IOP of <25 mm Hg (treatment with ≤3 IOP-lowering agents permitted)
Minimum time between treatments: minimum

Arm type	Active comparator
Investigational medicinal product name	Intravitreal Ranibizumab (Lucentis) 0.5 mg in 0.05 mL
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Emulsion for emulsion for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal ranibizumab (Lucentis) 0.5 mg in 0.05 mL Eligible eye(s) treated M01+ Retreatment required at M02, M03 if retreatment criteria met Retreatment permitted at M04 and later if retreatment criteria met
Retreatment criteria:
1) Central subfield thickness greater than 1.1 times the upper limit of normal (330 µm for Zeiss and Topcon SD OCT and 352 µm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield.

Number of subjects in period 1	Dexamethasone intravitreal implant 0.7mg	Intravitreal methotrexate 400µg in 0.1mL	Intravitreal ranibizumab 0.5mg in 0.05mL
Started	65	65	64
12 Week Primary outcome	64	63	61
Completed	60	59	58
Not completed	5	6	6
Lost to follow-up	5	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Dexamethasone intravitreal implant 0.7mg
Reporting group description:	
Dexamethasone intravitreal implant 0.7mg.Eligible eye(s) treated at study visit M01 (week 0). Retreatment required at study visit M03 (8 weeks) if re-treatment criteria met. Standard preparation as described for intravitreal injections. (Ozurdex®, Allergan, Irvine, CA)	
Reporting group title	Intravitreal methotrexate 400µg in 0.1mL
Reporting group description:	
Drug: Intravitreal Methotrexate 400 µg Intravitreal Methotrexate 400 µg injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to the injection.	
Reporting group title	Intravitreal ranibizumab 0.5mg in 0.05mL
Reporting group description:	
Intravitreal Ranibizumab 0.5 mg injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to the injection. (Lucentis®, Genentech Inc., San Francisco, CA) Eligible eye(s) treated at study visit M01 (week 0). Retreatment required at study visit M03 (8 weeks) if re-treatment criteria met. Retreatment permitted at later time points if retreatment criteria met. Re-treatment criteria: Central subfield thickness greater than 1.1X upper limit of normal (330 µm for Zeiss and Topcon Spectral Domain (SD) Optical Coherence Tomography (OCT) and 352 µm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield. IOP of <25 mm Hg (treatment with ≤3 IOP-lowering agents permitted) Minimum time between treatments: minimum	

Reporting group values	Dexamethasone intravitreal implant 0.7mg	Intravitreal methotrexate 400µg in 0.1mL	Intravitreal ranibizumab 0.5mg in 0.05mL
Number of subjects	65	65	64
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age in years at baseline			
Units: years			
median	59	59	57
full range (min-max)	18 to 81	20 to 83	24 to 83

Gender categorical Units: Subjects			
Female	41	48	40
Male	24	17	24
Race Units: Subjects			
Asian	10	10	8
Black	16	22	13
White	38	28	41
More than 1 race	0	1	0
Unknown race	1	4	2
Concomitant systemic medication			
Participant was on systemic medication for the treatment of macular edema or uveitis at baseline			
Units: Subjects			
Yes	28	27	29
No	37	38	35
Visual acuity			
Participants' visual acuity was measured by certified examiners with best refractive correction in place. Participants were challenged with reading letters on lines of the standard ETDRS eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until no more meaningful readings could be made and were scored by how many letters could be correctly identified. More letters read is associated with higher visual acuity. (85 standard letters = 20/20 vision)			
Units: Standard letters median full range (min-max)			
Intraocular pression (IOP) Units: mm Hg median full range (min-max)			
Retinal thickness at the center subfield			
Central subfield thickness as measured by OCT at a fundus photograph reading center			
Units: um median full range (min-max)			

Reporting group values	Total		
Number of subjects	194		
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			
Age in years at baseline			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	129		
Male	65		
Race			
Units: Subjects			
Asian	28		
Black	51		
White	107		
More than 1 race	1		
Unknown race	7		
Concomitant systemic medication			
Participant was on systemic medication for the treatment of macular edema or uveitis at baseline			
Units: Subjects			
Yes	84		
No	110		
Visual acuity			
Participants' visual acuity was measured by certified examiners with best refractive correction in place. Participants were challenged with reading letters on lines of the standard ETDRS eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until no more meaningful readings could be made and were scored by how many letters could be correctly identified. More letters read is associated with higher visual acuity. (85 standard letters = 20/20 vision)			
Units: Standard letters			
median			
full range (min-max)	-		
Intraocular pression (IOP)			
Units: mm Hg			
median			
full range (min-max)	-		
Retinal thickness at the center subfield			
Central subfield thickness as measured by OCT at a fundus photograph reading center			
Units: um			
median			
full range (min-max)	-		

Subject analysis sets

Subject analysis set title	Macular edema eyes from Arm 1 (Ozurdex)
Subject analysis set type	Per protocol
Subject analysis set description: Eyes with macular edema at baseline for Arm 1	
Subject analysis set title	Macular edema eyes in Arm 2 (Intravitreal Methotrexate)
Subject analysis set type	Per protocol
Subject analysis set description: Eyes with macular edema at baseline in Arm 2 (Intravitreal Methotrexate)	
Subject analysis set title	Macular edema eyes from Arm 3 Intravitreal Ranibizumab
Subject analysis set type	Per protocol

Subject analysis set description:
Eyes with macular edema at baseline for Arm 3 Intravitreal Ranibizumab

Reporting group values	Macular edema eyes from Arm 1 (Ozurdex)	Macular edema eyes in Arm 2 (Intravitreal Methotrexate)	Macular edema eyes from Arm 3 Intravitreal Ranibizumab
Number of subjects	77	79	69
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age in years at baseline			
Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
Asian Black White More than 1 race Unknown race			
Concomitant systemic medication			
Participant was on systemic medication for the treatment of macular edema or uveitis at baseline			
Units: Subjects			
Yes No			
Visual acuity			
Participants' visual acuity was measured by certified examiners with best refractive correction in place. Participants were challenged with reading letters on lines of the standard ETDRS eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until no more meaningful readings could be made and were scored by how many letters could be correctly identified. More letters read is associated with higher visual acuity. (85 standard letters = 20/20 vision)			
Units: Standard letters median full range (min-max)	 68 25 to 89	 64 6 to 85	 67 6 to 88
Intraocular pression (IOP) Units: mm Hg median	 15	 15	 14

full range (min-max)	5 to 21	5 to 23	7 to 21
Retinal thickness at the center subfield			
Central subfield thickness as measured by OCT at a fundus photograph reading center			
Units: um			
median	457	476	401
full range (min-max)	241 to 1116	276 to 991	220 to 1091

End points

End points reporting groups

Reporting group title	Dexamethasone intravitreal implant 0.7mg

Reporting group description:

Dexamethasone intravitreal implant 0.7mg.Eligible eye(s) treated at study visit M01 (week 0).
Retreatment required at study visit M03 (8 weeks) if re-treatment criteria met.
Standard preparation as described for intravitreal injections.
(Ozurdex®, Allergan, Irvine, CA)

Reporting group title	Intravitreal methotrexate 400µg in 0.1mL

Reporting group description:

Drug: Intravitreal Methotrexate 400 µg
Intravitreal Methotrexate 400 µg injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to the injection.

Reporting group title	Intravitreal ranibizumab 0.5mg in 0.05mL

Reporting group description:

Intravitreal Ranibizumab 0.5 mg injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to the injection.
(Lucentis®, Genentech Inc., San Francisco, CA)
Eligible eye(s) treated at study visit M01 (week 0).

Retreatment required at study visit M03 (8 weeks) if re-treatment criteria met.
Retreatment permitted at later time points if retreatment criteria met.
Re-treatment criteria:

Central subfield thickness greater than 1.1X upper limit of normal (330 µm for Zeiss and Topcon Spectral Domain (SD) Optical Coherence Tomography (OCT) and 352 µm for Heidelberg OCT) and/or cystoid space(s) within 1 mm central subfield.
IOP of <25 mm Hg (treatment with ≤3 IOP-lowering agents permitted)
Minimum time between treatments: minimum

Subject analysis set title	Macular edema eyes from Arm 1 (Ozurdex)
Subject analysis set type	Per protocol

Subject analysis set description:

Eyes with macular edema at baseline for Arm 1

Subject analysis set title	Macular edema eyes in Arm 2 (Intravitreal Methotrexate)
Subject analysis set type	Per protocol

Subject analysis set description:

Eyes with macular edema at baseline in Arm 2 (Intravitreal Methotrexate)

Subject analysis set title	Macular edema eyes from Arm 3 Intravitreal Ranibizumab
Subject analysis set type	Per protocol

Subject analysis set description:

Eyes with macular edema at baseline for Arm 3 Intravitreal Ranibizumab

Primary: Proportion of Baseline Central Subfield Thickness Observed at 12 Weeks

End point title	Proportion of Baseline Central Subfield Thickness Observed at 12 Weeks

End point description:

The primary outcome is the change in central subfield thickness from baseline to 12 weeks measured on a relative scale as the the proportion of the baseline central subfield thickness. Values less than 1 indicate a decrease in retinal thickness with lower values indicating greater decreases. Smaller values are better The assessment of OCT outcomes was performed by masked readers.

End point type	Primary

End point timeframe:

The 12-week visit was chosen as the time to assess the primary outcome because the ranibizumab treatment arm specifies injections at baseline, 4 weeks and 8 weeks in all participants, and because the peak benefit for the dexamethasone pellet appears to be

End point values	Dexamethasone intravitreal implant 0.7mg	Intravitreal methotrexate 400µg in 0.1mL	Intravitreal ranibizumab 0.5mg in 0.05mL	Macular edema eyes from Arm 1 (Ozurdex)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0[1]	0[2]	0[3]	77
Units: Proportion of baseline retinal thickness				
arithmetic mean (confidence interval 95%)	(to)	(to)	(to)	0.65 (0.58 to 0.72)

Notes:

[1] - analyzed eyes with ME

[2] - Analyzed eyes with ME

[3] - Analyzed eyes with ME

End point values	Macular edema eyes in Arm 2 (Intravitreal Methotrexate)	Macular edema eyes from Arm 3 Intravitreal Ranibizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	69		
Units: Proportion of baseline retinal thickness				
arithmetic mean (confidence interval 95%)	0.88 (0.81 to 0.96)	0.79 (0.70 to 0.89)		

Statistical analyses

Statistical analysis title	Methotrexate compared to Ozurdex

Statistical analysis description:

Mixed model was used to determine the treatment effect as the ratio of the proportions of baseline retinal thickness (Lucentis/Ozurdex) at 12 weeks. Values greater than 1 indicate less reduction in retinal thickness in the methotrexate treated group compared to Ozurdex

Comparison groups	Macular edema eyes from Arm 1 (Ozurdex) v Macular edema eyes in Arm 2 (Intravitreal Methotrexate)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Ratio of proportion of baseline
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.56

Notes:

[4] - Ozurdex (0.7 mg Dexamethasone Pellet) Delivered Via Intravitreal Injection, Intravitreal Methotrexate 400 µg in 0.1 mL 0.9% Sodium Chloride Solution, Preservative-free

Statistical analysis title	Lucentis compared to Ozurdex

Statistical analysis description:

Ozurdex (0.7 mg Dexamethasone Pellet) Delivered Via Intravitreal Injection, Intravitreal Ranibizumab (Lucentis) 0.5 mg in 0.05 mL
Comments
The treatment effect is the ratio of the proportions of baseline retinal thickness (Lucentis/Ozurdex) at 12 weeks. Values greater than 1 indicate less reduction in retinal thickness in the Lucentis treated group compared to Ozurdex estimated by a mixed model

Comparison groups	Macular edema eyes from Arm 1 (Ozurdex) v Macular edema eyes from Arm 3 Intravitreal Ranibizumab
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 [5]
Method	Mixed models analysis
Parameter estimate	Ratio of the proportion of baseline
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.43

Notes:

[5] - Bonferroni correction was used to adjust for the co-primary hypotheses;a two-sided type I error rate of 0.05/2 = 0.025 was used to determine statistical significance for the two pairwise comparisons (Ozurdex vs Methotrexate and Ozurdex vs Lucentis)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events over 24 weeks

Adverse event reporting additional description:

Serious adverse events were reported via an expediated reporting system followed by medical safety review. Non-serious events collected in non-systemic means via an adverse event log that was completed at each visit and by systemic collection of information on ocular events of special interest on the follow up visit case reform forms.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Arm 1 Ozurdex (Demamethasone)

Reporting group description: -

Reporting group title	Arm 2 Intravitreal methotrexate

Reporting group description:

Intravitreal methotrexate 400 µg in 0.1 mL Eligible eye(s) treated at week 0 Retreatment required at M02, M03 if retreatment criteria met Retreatment permitted at M04 and later if retreatment criteria met

Reporting group title	Arm 3 Intravitreal ranibizumab (Lucentis)

Reporting group description:

Intravitreal ranibizumab (Lucentis) 0.5 mg in 0.05 mL Eligible eye(s) treated M01+ Retreatment required at M02, M03 if retreatment criteria met Retreatment permitted at M04 and later if retreatment criteria met

Serious adverse events	Arm 1 Ozurdex (Demamethasone)	Arm 2 Intravitreal methotrexate	Arm 3 Intravitreal ranibizumab (Lucentis)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 65 (15.38%)	10 / 65 (15.38%)	3 / 64 (4.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast caner			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
post procedure infection			

subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vasovagal response			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Catheterization cardiac for hypertension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Intraocular pressure decreased			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased			
subjects affected / exposed	3 / 65 (4.62%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iridotomy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

visual acuity decreased			
subjects affected / exposed	0 / 65 (0.00%)	5 / 65 (7.69%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
glaucoma			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal oedema			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma surgery			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Arm 1 Ozurdex (Demamethasone)	Arm 2 Intravitreal methotrexate	Arm 3 Intravitreal ranibizumab (Lucentis)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 65 (35.38%)	29 / 65 (44.62%)	20 / 64 (31.25%)
Investigations			
Intraocular pressure decreased			
subjects affected / exposed	3 / 65 (4.62%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Intraocular pressure fluctuation	Additional description: Following treatment injection IOP was increased > than 30 mm Hg temporary		
subjects affected / exposed	0 / 65 (0.00%)	12 / 65 (18.46%)	6 / 64 (9.38%)
occurrences (all)	0	24	14
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	2 / 65 (3.08%)	0 / 64 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
headache			
subjects affected / exposed	1 / 65 (1.54%)	2 / 65 (3.08%)	4 / 64 (6.25%)
occurrences (all)	1	4	4
Eye disorders			
Eye pain			
subjects affected / exposed	8 / 65 (12.31%)	5 / 65 (7.69%)	5 / 64 (7.81%)
occurrences (all)	13	9	7
Ocular hypertension			
subjects affected / exposed	2 / 65 (3.08%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	3	2	0
surgery to control IOP			
subjects affected / exposed	1 / 65 (1.54%)	4 / 65 (6.15%)	0 / 64 (0.00%)
occurrences (all)	1	5	0
Uveitis			
subjects affected / exposed	2 / 65 (3.08%)	2 / 65 (3.08%)	2 / 64 (3.13%)
occurrences (all)	2	2	2
Vitreous haemorrhage			
subjects affected / exposed	3 / 65 (4.62%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	3	0	1
Vitreous floaters			

subjects affected / exposed	2 / 65 (3.08%)	4 / 65 (6.15%)	1 / 64 (1.56%)
occurrences (all)	3	5	2
Chalazion			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	1	1	0
Conjunctival haemorrhage			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	2	0	1
Dry eye			
subjects affected / exposed	2 / 65 (3.08%)	1 / 65 (1.54%)	2 / 64 (3.13%)
occurrences (all)	3	2	2
Eyelid oedema			
subjects affected / exposed	2 / 65 (3.08%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	2	1	0
Photopsia			
subjects affected / exposed	4 / 65 (6.15%)	2 / 65 (3.08%)	0 / 64 (0.00%)
occurrences (all)	6	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	0 / 65 (0.00%)	2 / 65 (3.08%)	1 / 64 (1.56%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	2 / 64 (3.13%)
occurrences (all)	1	1	3
Arthritis			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	0 / 64 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	1	0	2
Nasopharyngitis			

subjects affected / exposed	0 / 65 (0.00%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	1 / 64 (1.56%)
occurrences (all)	1	0	1
Sinusitis			
subjects affected / exposed	2 / 65 (3.08%)	1 / 65 (1.54%)	1 / 64 (1.56%)
occurrences (all)	2	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	2 / 64 (3.13%)
occurrences (all)	1	0	2
Urinary track infection			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	0 / 64 (0.00%)
occurrences (all)	2	0	0

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? Yes

Date	Interruption	Restart date
16 March 2020	Enrollment was temporarily suspended due to the COVID-19 pandemic on 16 Mar 2020. Enrollment was permitted to resume on a clinic-by-clinic basis begining 23 Jul 2023.	23 July 2020

Notes:

Limitations and caveats

None reported