Clinical trial results:
Efficacy and safety of dexamethasone nanoparticles eye drops in diabetic macular edema.

Summary

EudraCT number	2017-001172-36
Trial protocol	SE DK FI HU LV EE
Global end of trial date	28 March 2019

Results information

Result version number	v1 (current)
This version publication date	19 April 2020
First version publication date	19 April 2020
Summary attachment (see zip file)	Oculis_EU Clinical Trials Register_DX211 (Oculis_EU Clinical Trials Register_DX211.pdf)

Trial information

Trial identification

Sponsor protocol code	DX-211

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Oculis
Sponsor organisation address	Alfheimar 74, Reykjavik, Iceland, 104
Public contact	Riad Sherif, Oculis ehf., riad.sherif@oculis.com
Scientific contact	Fabio Baschiera, Oculis ehf., fabio.baschiera@oculis.com

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	08 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2019
Global end of trial reached?	Yes
Global end of trial date	28 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Compare the effects of DexNP eye drops with eye drops containing vehicle on visual acuity and central macular thickness (CMT) in subjects with DME over 12 weeks.
2. Mean change in CMT as assessed by Spectral Domain Optical Coherence Tomography (SD-OCT) at Weeks 2, 4, 8, 12, and 16 compared to baseline;
3. Monitor safety of the DexNP eye drop suspension treatment over 12 weeks.

Protection of trial subjects:

A 12-week treatment with monthly visits in recent-onset DME patients was deemed acceptable. DME rescue treatment criteria were listed in the protocol in case of
• IOP rise
• BCVA worsening
• Upon investigator discretion
A 4-week Follow up without study treatment was performed for all patients.

Background therapy:

No

Evidence for comparator:

NA

Actual start date of recruitment	18 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Estonia: 20
Country: Number of subjects enrolled	Finland: 20
Country: Number of subjects enrolled	Hungary: 61
Country: Number of subjects enrolled	Latvia: 8
Worldwide total number of subjects	144
EEA total number of subjects	144

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)	67
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 184 patients were screened and 144 were treated. The ITT , the Per Protocol and the Safety Set population consist of 144 patients.

Pre-assignment

Screening details:

1. Had DME of less than 3 years duration since diagnosis
2. Had an ETDRS BCVA letter score between 73 and 24 in the study eye at baseline

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Subject in Active arm received 1 DexNP eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	DexNP1.5%
Investigational medicinal product code	DexNP
Other name	Dexamethasone nanoparticle eye drops
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ophthalmic use

Dosage and administration details:

1 DexNP eye drop in the study eye 3 times a day (every 8 hours) for 12 weeks

Arm title	Vehicle

Arm description:

Subjects received vehicle eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	NA
Other name	NA
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ophthalmic use

Dosage and administration details:

Subjects received vehicle eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks.

Number of subjects in period 1	Active	Vehicle
Started	99	45
Completed	91	42
Not completed	8	3
Consent withdrawn by subject	1	1
Adverse event, non-fatal	3	1
Other	3	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Subject in Active arm received 1 DexNP eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks	
Reporting group title	Vehicle
Reporting group description:	
Subjects received vehicle eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks.	

Reporting group values	Active	Vehicle	Total
Number of subjects	99	45	144
Age categorical			
Age Category (years), n (%)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
<50	9	4	13
50-70	60	21	81
≥70	30	20	50
Age continuous			
Age			
Units: years			
arithmetic mean	63.0	65.8	
full range (min-max)	30 to 77	35 to 76	-
Gender categorical			
Male/female (n)			
Units: Subjects			
Female	35	17	52
Male	64	28	92

Subject analysis sets	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Consisted of all randomized subjects, analysed subjects under the treatment to which they were randomized (V2).	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Included all randomized subjects who received at least one dose of study medication.	

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

It is a subset of the ITT population and included subjects who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study, analyzed subjects under the treatment actually received.

Reporting group values	ITT population	Safety Set	Per Protocol Set
Number of subjects	144	144	144
Age categorical			
Age Category (years), n (%)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
<50	13	13	13
50-70	81	81	81
≥70	50	50	50
Age continuous			
Age			
Units: years			
arithmetic mean	64.4	64.4	64.4
full range (min-max)	33 to 85	33 to 85	33 to 85
Gender categorical			
Male/female (n)			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Active
Reporting group description:	
Subject in Active arm received 1 DexNP eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks	
Reporting group title	Vehicle
Reporting group description:	
Subjects received vehicle eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks.	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Consisted of all randomized subjects, analysed subjects under the treatment to which they were randomized (V2).	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Included all randomized subjects who received at least one dose of study medication.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
It is a subset of the ITT population and included subjects who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study, analyzed subjects under the treatment actually received.	

Primary: Primary endpoint of the study is mean change in ETDRS Best corrected visual acuity (BCVA) letters at Week 12 compared to baseline.

End point title	Primary endpoint of the study is mean change in ETDRS Best corrected visual acuity (BCVA) letters at Week 12 compared to baseline.
End point description:	
Primary endpoint of the study is mean change in ETDRS Best corrected visual acuity (BCVA) letters at Week 12 compared to baseline.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Active	Vehicle	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	99[1]	45[2]	144[3]	
Units: ETDRS				
number (not applicable)	2.62	1.04	144	

Notes:

[1] - DexNP

[2] - Vehicle

[3] - ITT population

Statistical analyses

Statistical analysis title	Change from Baseline in ETDRS BCVA

Statistical analysis description:

The statistical hypotheses for the primary endpoint of mean change from baseline in ETDRS BCVA letters in the study eye at Week 12. The study was to be considered a success and DexNP superior to Vehicle if the one-sided p-value was less than 0.15 and the difference in mean change from baseline ETDRS BCVA letters was greater than 0.

Comparison groups	Active v Vehicle v ITT population
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	≤ 0.15 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	Other: 70 %
sides	1-sided
lower limit	0
Variability estimate	Standard error of the mean

Notes:

[4] - The primary analysis of the primary endpoint employed a linear model with change from baseline ETDRS BCVA letters as the response, baseline ETDRS BCVA letters as a covariate, and treatment as a main effect factor, using the ITT population and with multiple imputation pattern mixture model techniques used to impute missing data.
Analysis of covariance (ANCOVA) provided a method for comparing response means among two treatment groups adjusted for baseline values as a covariate only.
[5] - The study was to be considered a success and DexNP superior to Vehicle if the one-sided p-value was less than 0.15 and the difference in mean change from baseline ETDRS BCVA letters was greater than 0.

Secondary: Central Macular Thickness

End point title	Central Macular Thickness

End point description:

The endpoint was analyzed similarly to the primary efficacy analyses using ODO (Observed Data Only) on the ITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Active	Vehicle	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	99	45	144	
Units: Micrometer				
least squares mean (confidence interval 70%)	-53.68 (-62.980 to -44.380)	-16.87 (-30.812 to -2.935)	-36.81 (-53.576 to -20.038)	

Statistical analyses

Statistical analysis title	CMT Changes from Baseline
Statistical analysis description:	
Statistical Analysis of Change from Baseline in Study Eye Central Macular Thickness using Multiple Imputation (Intent-to-Treat Population)	
Comparison groups	Active v Vehicle v ITT population
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	≤ 0.15 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	Other: 70 %
sides	1-sided
lower limit	0.15

Notes:

[6] - Descriptive

[7] - The study was to be considered a success and DexNP superior to Vehicle if the one-sided p-value was less than 0.15 and the difference in mean change from baseline ETDRS BCVA letters was greater than 0.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 SEP 2017 to 28 MAR 2019

Adverse event reporting additional description:

An AE was classified as pre-Treatment AE if it started before the first randomized study medication intake (AE onset date < date of first randomized study medication intake).
An AE was classified as a treatment emergent AE (TEAE) if the AE onset date was following the constraint.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	DexNP Eye drops
Reporting group description: -	
Reporting group title	Vehicle Eye drops

Reporting group description:

Placebo group

Serious adverse events	DexNP Eye drops	Vehicle Eye drops	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 99 (11.11%)	1 / 45 (2.22%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 99 (2.02%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 99 (2.02%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Death	Additional description: 1 Death 1 Sudden cardiac death		
subjects affected / exposed	2 / 99 (2.02%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetic ulcer			
subjects affected / exposed	1 / 99 (1.01%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza like illnessence			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DexNP Eye drops	Vehicle Eye drops	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 99 (70.71%)	24 / 45 (53.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 99 (3.03%)	2 / 45 (4.44%)	
occurrences (all)	3	2	
peripheral arterial occlusive disease			
subjects affected / exposed	2 / 99 (2.02%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	1 / 99 (1.01%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	4 / 99 (4.04%)	0 / 45 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 99 (1.01%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	24 / 99 (24.24%)	0 / 45 (0.00%)	
occurrences (all)	26	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 99 (2.02%)	0 / 45 (0.00%)	
occurrences (all)	2	0	

Blood pressure increased			
subjects affected / exposed	2 / 99 (2.02%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	1 / 99 (1.01%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 99 (2.02%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Cardiac failure			
subjects affected / exposed	2 / 99 (2.02%)	1 / 45 (2.22%)	
occurrences (all)	2	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 99 (3.03%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Blood and Lymphatic system disorders			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	1 / 99 (1.01%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diabetic retinal oedema			
subjects affected / exposed	70 / 99 (70.71%)	24 / 45 (53.33%)	
occurrences (all)	134	50	
Eye irritation			
subjects affected / exposed	3 / 99 (3.03%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Ocular hypertension			
subjects affected / exposed	3 / 99 (3.03%)	1 / 45 (2.22%)	
occurrences (all)	3	1	

Visual acuity reduced subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3	2 / 45 (4.44%) 2	
Cataract subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2	1 / 45 (2.22%) 1	
Diabetic retinopathy subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 3	0 / 45 (0.00%) 0	
Visual acuity reduced transiently subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2	0 / 45 (0.00%) 0	
Vitreous haemorrhage subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2	0 / 45 (0.00%) 0	
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	2 / 45 (4.44%) 2	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	4 / 99 (4.04%) 3	0 / 45 (0.00%) 0	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3	1 / 45 (2.22%) 2	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 2	0 / 45 (0.00%) 0	
Musculoskeletal and connective tissue disorders muscolo skeletal and connective tissue disorders subjects affected / exposed occurrences (all)	4 / 99 (4.04%) 4	1 / 45 (2.22%) 1	
Infections and infestations			

Influenza			
subjects affected / exposed	4 / 99 (4.04%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Nasopharyngitis			
subjects affected / exposed	4 / 99 (4.04%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 99 (3.03%)	1 / 45 (2.22%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2018	Protocol Amendment #1: a) The number of subjects was increased from 96 to 144 subjects. b) The statistical power increased from 80% to c) 90%. d) The number of sites participating in the study e) has been increased from 13 to approximately 27. f) Addition of subgroup analysis of anti-VEGF nonresponders, increased the Sample Size. g) Remove interim analysis. h) Minor changes were done throughout the protocol

Notes:

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.

Exploratory study p value

Notes: