EFFICACY AND SAFETY OF DEXAMETHASONE NANOPARTICLES EYE DROPS IN DIABETIC MACULAR EDEMA

Study Information	
Sponsor:	Oculis ehf Alfheimar 74, 6th Floor 104 Reykjavik Iceland +354 546 4440
Sponsor Study/Protocol No.	DX-211
Additional study identifiers	EudraCT Number: 2017-001172-36
Study Drug/Product Name:	DexNP 15 mg/mL
Development Phase:	Phase IIb
Indication:	Diabetic Macular Edema

Trial information	
Study Title:	EFFICACY AND SAFETY OF DEXAMETHASONE NANOPARTICLES EYE DROPS IN DIABETIC MACULAR EDEMA
Date of First Enrollment:	18 Sep 2017
Date of Last Subject Completed:	28 Mar 2019
Public contact, Oculis:	Riad Sherif, CEO: riad.sherif@oculis.com
Study Director, Oculis:	Fabio Baschiera, VP Clinical Development: fabio.baschiera@oculis.com
Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004	No
Analysis stage	
Date of interim/final analysis:	08 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2019
Was the trial ended prematurely?	No
Global end of trial reached?	Yes
Global end of trial date	28 March 2019

General information about the trial	
Study design	Prospective, multi-center, randomized, double-masked, parallel group, vehicle suspension-controlled study.
Main objective(s) 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. 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/end date of recruitment	18 September 2017 to 28 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No
Changes in Study conduct	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

Study Design/Methodology

This was a prospective, Phase IIb, multi-center, randomized, double-masked, parallel group, vehicle suspension-controlled study. Approximately 144 eligible subjects were to be randomized in the study. The study consisted of 4 phases:

- Screening phase
- Randomization phase
- Treatment phase
- Follow-up phase

Subjects were randomized in a 2:1 ratio; in one arm subjects received 1 DexNP eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks and in the other arm subjects received vehicle eye drops in the study eye 3 times a day (every 8 hours) for 12 weeks.

Primary efficacy assessments were performed at Week 12. A safety follow-up was performed after 4 weeks of last dose of study treatment.

Centers

27 centers in 6 countries: Sweden (6), Denmark (4), Finland (2), Hungary (9), Estonia (5), Latvia (1).

Population of trial subjects	
Subjects enrolled per country	
Sweden	18
Denmark	17
Finland	20
Hungary	61
Estonia	20
Latvia	8
Worldwide total number of subjects	144
EEA total number of subjects	144
Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 0 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	67
From 65 to 85 years	77
86 years and over	0

Publication

Primary manuscript in preparation.

Study Objectives

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.

Test Product (s), Dose(s), and Mode(s) of Administration

1. DexNP1.5% suspension 3 times daily for 3 weeks
2. Vehicle 3 times daily for 3 weeks

Arm title: DexNP

Arm description: DexNP 3 drops x day

Arm type: Experimental

Investigational medicinal product name: Dexamethasone Nanoparticles

Investigational medicinal product code: OC-118

Other name: OCS-01

Pharmaceutical forms: Suspension

Routes of administration: topical eye drops

Reference Product(s), Dose(s), and Mode(s) of Administration

Arm title: Vehicle

Arm description: Vehicle 3 drops daily

Arm type: Comparator, Placebo

Investigational medicinal product name: NA

Investigational medicinal product code: NA

Other name: NA

Pharmaceutical forms: Suspension

Routes of administration: topical exe drops

Statistical Methods

Descriptive statistics for quantitative endpoints included n (the number of non-missing values), arithmetic mean, standard deviation (SD), median, minimum and maximum values. The primary efficacy endpoint (change from baseline in ETDRS BCVA letters to Week 12) was summarised using continuous summary statistics, including the 70%, 90% and 95% confidence intervals (CIs) of the arithmetic mean for each treatment group. Hypothesis testing was carried out at the alpha=0.15 level (one-sided). Statistical significance was declared if the p-value was less than 0.15.

Study Analysis Populations

Safety Population

Included all randomized subjects who received at least one dose of study medication. The safety population was analysed as treated and was used for the safety analyses. No data was excluded for any reason.

Intent-to-Treat Population (ITT)

Consisted of all randomized subjects, analysed subjects under the treatment to which they were randomized (V2).

Per-Protocol Population

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. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment were identified prior to unmasking treatment.

The primary efficacy endpoint was analysed both in the ITT and in the PP populations.

The secondary efficacy endpoints were analysed in the ITT population only.

Primary Efficacy Endpoint Methodology

Change from Baseline in ETDRS Best Corrected Visual Acuity Letters at Week 12

The statistical hypotheses for the primary endpoint of mean change from baseline in ETDRS BCVA letters in the study eye at Week 12 were as follows:

- H0: The difference between study eyes treated with DexNP and study eyes treated with Vehicle (DexNP – Vehicle) in the mean change from baseline ETDRS BCVA letters to Week 12 (Week 12 – Baseline) ≤ 0;
- H1: The difference between study eyes treated with DexNP and study eyes treated with Vehicle (DexNP – Vehicle) in the mean change from baseline ETDRS BCVA letters to Week 12 (Week 12 – Baseline) > 0.

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.

The primary efficacy endpoint was summarized by treatment group using descriptive statistics, including 70%, 90% and 95% CIs. Change from baseline to Visit 6 (Week 12) was also summarised by treatment group.

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, thought to influence the response.

Analyses were secondarily completed using a two-sample t-test.

The least squared mean, standard error, and 70%, 90% and 95% CIs for each treatment group, and the difference between treatment groups, were presented as well as a 1-sided p-value testing the difference versus the null hypothesis value of 0.

Subjects who received rescue medication prior to Week 12 had their Week 12 measure replaced with their last observation prior to receiving rescue medication.

To check the robustness of primary efficacy analysis results, the previously described analyses of the primary efficacy measures were repeated based on alternate handlings of missing data analysis populations. The ITT population using observed data only (ODO), last observation carried forward (LOCF), and baseline observation carried forward (BOCF).

Additionally, a subgroup analysis on the primary efficacy endpoint were performed based on subset of subjects (whether they had received anti-VEGF treatment or not in the past)

The primary efficacy analyses using multiple imputation and ODO was also secondarily completed on the PP population.

In all of these analyses, subjects who received rescue medication prior to Week 12 had their Week 12 measure replaced with their last observation prior to receiving rescue medication.

Secondary Efficacy Endpoint Methodology

Mean Change in CMT as Assessed by SD-OCT at Weeks 2, 4, 8, 12, And 16 Compared to Baseline was analyzed similarly to the primary efficacy analyses using ODO on the ITT population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Subjects must have met all of the following criteria for inclusion in the study:

1. Had DME of less than 3 years duration since diagnosis with presence of intraretinal and/or subretinal fluid in the study eye, with CMT of ≥ 310 µm by SD-OCT at baseline (Visit 2) (as measured by the Investigator).
2. Had definite retinal thickening in the study eye due to DME involving the central macula based on the Investigator's clinical evaluation and by SD-OCT;

   Note: If the DME consisted of circumscribed, focal leakage that the evaluating Investigator believes should be treated with laser and no other treatments, the eye was not eligible to be a study eye.
3. Had an ETDRS BCVA letter score ≤ 73 (Snellen 20/40) and ≥ 24 (Snellen 20/320) in the study eye at baseline (Visit 2).
4. Had a documented diagnosis of type 1 or type 2 diabetes mellitus and a HbA1c of ≤ 12.0% at Visit 1.
5. Had a negative urine pregnancy test at Visit 1. If female of childbearing potential those who had experienced menarche and who were not surgically sterilized (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) as well as post-menopausal (12 months after last menses) females had to use adequate birth control throughout the study period. Adequate birth control was defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner. For non- sexually active females, abstinence could be regarded as an adequate method of birth control.
6. Agree to not participate in another interventional study after providing informed consent and until the study was completed.

7. Provided written informed consent prior to any study procedure being performed and was able and willing to follow all instructions and attended all study visits.
8. Were18 to 85 years of age at Screening Visit (Visit 1), of either sex and any race or ethnicity.

Exclusion Criteria

Subjects who met any of the following exclusion criteria were not included in the study:

1. Had macular edema considered to be due to a cause other than DME;
   Note: An eye was not considered eligible if: (1) the macular edema was considered to be related to ocular surgery such as cataract extraction;(2) clinical exam and/or OCT suggested that vitreoretinal interface abnormalities disease (e.g., a taut posterior hyaloid or epiretinal membrane) was the primary cause of the macular edema, or (3) the macular edema was considered to be related to another condition such as age-related macular degeneration, uveitis, retinal vein occlusion, or drug toxicity.
2. Had a decrease in BCVA due to causes other than DME (e.g., foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, previous vitreoretinal surgery, central serous retinopathy, non-retinal condition, substantial cataract, macular ischemia) that is likely to be decreasing BCVA by 3 lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal).
3. Had significant macular ischemia, as assessed by the Investigator, which in the opinion of the investigator would prevent gain in visual acuity.
4. Had any other ocular disease that could cause substantial reduction in BCVA, including, retinal detachment, epiretinal membrane, vitreous hemorrhage or fibrosis involving the macula in the study eye, ocular inflammation (uveitis), other retinal inflammatory or infectious diseases
5. Had active peri-ocular or ocular infection (e.g., blepharitis, keratitis, scleritis, or conjunctivitis)
6. Had a history of non-infectious uveitis
7. Had high myopia (-8 diopter or more correction) in the study eye
8. Wore contact lenses during the 12-week active treatment study period
9. Had a history of any ocular surgery in the study eye within 3 months prior to Visit 1;
10. Had a history of Yttrium-Aluminum-Granate laser capsulotomy in the study eye, within 3 months prior to Visit 1;
11. Had a history of panretinal scatter photocoagulation (PRP) or focal laser within 3 months prior to Visit 1 or an anticipated need for PRP during the course of the study in the study eye;
12. Used other ophthalmic formulations during the study. However, intraocular pressure (IOP) lowering eye drops were allowed if they became necessary due to increased IOP.
13. Had a history of prior intravitreal (IVT), subtenon, or periocular, non-sustained release, steroid therapy in the study eye within 3 months prior to Visit 1 (e.g., triamcinolone)
14. Had a history of intravitreal sustained release dexamethasone therapy in the study eye within 6 months prior to Visit 1;
15. Had a history of intravitreal sustained release fluocinolone in the study eye within 3 years prior to Visit 1;
16. Had a history of prior treatment of intravitreal (IVT) aflibercept in the study eye within 8 weeks and ranibizumab/bevacizumab within 6 weeks of Visit 1;
17. Had a history of prior treatment for DME in the study eye with any other (than previously listed) approved treatment, which is not labeled for DME within one year prior to Visit 1;

18. Had high-risk proliferative diabetic retinopathy in the study eye, defined in the ETDRS study as at least one of the following:
- New vessels within one-disc diameter of the optic disc (NVD) ≥ 1/3 disc area;
- Any NVD with vitreous or pre-retinal hemorrhage;
- New vessels elsewhere in the retina ≥ ½ disc area and pre-retinal or vitreous hemorrhage;

19. Had uncontrolled ocular hypertension or glaucoma in either eye, defined as IOP ≥ 22 mmHg on more than 1 IOP lowering medications at Visit 1
20. Hade poor media clarity, pupillary constriction (i.e., senile miosis), or lack cooperation that, in the opinion of the evaluating Investigator, would interfere with any study procedures, evaluations, or interpretation of data
21. Hade any ocular condition that, in the opinion of the Investigator, may require intervention, interfere with evaluations of efficacy or safety or interpretation of data collected in the study
22. Hade an estimated Glomerular Filtration Rate of < 15mL/min/1.73m2 as per CKD-EPI equation at Visit 1
23. Hade a systolic blood pressure < 90 or > 160 mmHg and / or a diastolic blood pressure > 100 mmHg at Visit 1
24. Hade a known or suspected hypersensitivity to any components of the test agent
25. Be a female subject who was pregnant or lactating or had a positive pregnancy test at Visit 1 or had been pregnant within 6 months before Visit 1 or breast-feeding within 3 months before Visit 1, or planning to become pregnant within 9 months from Visit 1
26. Hade participated in any interventional clinical study or been treated with any investigational drugs within 30 days or 5 half-lives of the investigational drug, whichever was longer, prior to the initiation of Visit 1.
27. Hade any other condition, which in the opinion of the evaluating Investigator, precludes the subject's participation in the trial.

Number of Subjects (Randomized set)

	DexNP Eye Drop	Vehicle Eye Drop	Overall
Number of Screened Subjects			184
Number of Screen Failures			40
Number of Randomized Subjects	99	45	144 (78.3)
Number of Completed Subjects	91 (91.9)	42 (93.3)	133 (92.4)
Number of Discontinued Subjects	8 (8.1)	3 (6.7)	11 (7.6)
Reason for Discontinuation from Study			
Subject Withdrawn	1 (1.0)	1 (2.2)	2 (1.4)

Demographic Characteristics (Safety Population)

	DexNP Eye Drop (N=99)	Vehicle Eye Drop (N=45)	Overall (N=144)
Age (years)			
n	99	45	144
Mean (SD)	63.6 (9.50)	66.1 (9.92)	64.4 (9.67)
Median	64.0	69.0	65.0
Min, Max	33, 85	36, 80	33, 85
Age Category (years), n (%)			
<50	9 (9.1)	4 (8.9)	13 (9.0)
50-70	60 (60.6)	21 (46.7)	81 (56.3)
≥70	30 (30.3)	20 (44.4)	50 (34.7)
Gender (n (%)			
Male	64 (64.6)	28 (62.2)	92 (63.9)
Female	35 (35.4)	17 (37.8)	52 (36.1)
Race (n (%)			
Asian	1 (1.0)	0	1 (0.7)
Caucasian	98 (99.0)	45 (100)	143 (99.3)

Abbreviations: Min=Minimum; Max=Maximum; SD=Standard deviation
Notes: Age is calculated as the number of complete years between subject's birth date and the date of informed consent.

Baseline Characteristics (Safety Population)

	DexNP Eye Drop (N=99)	Vehicle Eye Drop (N=45)	Overall (N=144)
ETDRS BCVA Letter Score at Baseline			
n	99	45	144
Mean (SD)	63.0 (9.78)	65.8 (8.25)	63.9 (9.39)
Median	66.0	68.0	67.0
Min, Max	30, 77	35, 76	30, 77
Central Macular Thickness (CMT) at Baseline			
n	99	45	144
Mean (SD)	471.8 (140.18)	448.5 (117.80)	464.5 (133.61)
Median	424.0	413.0	422.5
Min, Max	234, 896	241, 712	234, 896
Intraocular Pressure (IOP) at Baseline			
n	99	45	144
Mean (SD)	15.3 (3.02)	14.7 (3.66)	15.1 (3.23)
Median	16.0	15.0	15.5
Min, Max	8, 24	7, 22	7, 24
Diabetes Mellitus (DM) Type (n (%))			
Type 1	11 (11.1)	1 (2.2)	12 (8.3)
Type 2	86 (86.9)	44 (97.8)	130 (90.3)
Not Stated	2 (2.0)	0	2 (1.4)
Years of Diabetes Mellitus (DM)			
n	48	23	71
Mean (SD)	15.78 (11.645)	15.17 (7.920)	15.58 (10.529)
Median	15.19	15.91	15.87
Min, Max	0.9, 48.9	0.9, 27.6	0.9, 48.9
Years of Diabetic Macular Edema (DME)			
n	99	45	144
Mean (SD)	1.20 (1.168)	1.60 (2.506)	1.33 (1.704)

Median	0.88	1.01	0.95
Min, Max	0.016, 7.135	0.025, 16.723	0.016, 16.723

Abbreviations: ETDRS BCVA= Early Treatment of Diabetic Retinopathy Study best-corrected visual; Min=Minimum; Max=Maximum; SD=Standard deviation.
Notes: ETDRS BCVA letter scores, CMT and IOP values and years of DME are presented for study eyes only; Duration of DM and DME calculated based on subject's medical history; Duration is calculated as the number of complete years between start and end dates for the relevant disease; Ongoing disease imputed with the date of randomisation for the missing end dates.

Primary Objective Result(s)

Statistical Analysis of Change from Baseline to Week 12 in Study Eye ETDRS BCVA Letters using Multiple Imputation (Intent-to-Treat Population)

	DexNP Eye Drop (N=99)	Vehicle Eye Drop (N=45)	p-value
Number of Subjects Included in Model	99	45	
Effects			
Treatment			0.1258
ETDRS BCVA letters at Baseline			0.1721
LS Mean			
Estimate (SE)	2.62 (0.7582)	1.04 (1.1113)	
Two-sided (70% CI)	(1.831, 3.403)	(-0.115, 2.189)	
Two-sided (90% CI)	(1.369, 3.865)	(-0.792, 2.865)	
Two-sided (95% CI)	(1.129, 4.104)	(-1.142, 3.216)	
Difference in LS Means			
DexNP - Vehicle	1.58		0.1258
Two-sided (70% CI)	(0.151, 3.009)		
Two-sided (90% CI)	(-0.688, 3.849)		
Two-sided (95% CI)	(-1.124, 4.284)		
Student's two-sample T-test:			
Mean Difference	1.75		0.0993
Two-sided (70% CI)	(0.340, 3.168)		
Two-sided (90% CI)	(-0.491, 3.999)		
Two-sided (95% CI)	(-0.922, 4.430)		

Abbreviations: ETDRS BCVA= Early Treatment of Diabetic Retinopathy Study best-corrected visual acuity; CI=Confidence Interval; LS=Least square; SE=Standard Error

Statistical analysis of change from baseline in study eye ETDRS BCVA letters using multiple imputation in the PP Population was performed similarly as the primary endpoint analysis.

A total of 94 subjects in the DexNP arm and 41 subjects in the Vehicle arm were included in the PP Population. Reason for exclusion of subjects from the PP.

The ANCOVA results showed a statistically non-significant effect of the treatment (LS Mean change=1.52 (70% CI -0.036, 3.071), one sided p-value=0.155 at alpha=0.15) in the change from baseline of ETDRS BCVA letters when the ETDRS BCVA letters at baseline was included as a covariate in the model. The between treatment difference in PP Population (LS mean difference

Secondary Objective Result(s)

Statistical Analysis of Change from Baseline in Study Eye Central Macular Thickness using Multiple Imputation (Intent-to-Treat Population)

	DexNP Eye Drop (N=99)	Vehicle Eye Drop (N=45)	p-value
Number of Subjects Included in Model	99	45	
Effects			

Treatment			0.0115
Central Macular Thickness at Baseline			<0.001
LS Mean			
Estimate (SE)	-53.68 (8.9723)	-16.87 (13.4459)	
Two-sided (70% CI)	(-62.980, -44.380)	(-30.812, -2.935)	
Two-sided (90% CI)	(-68.441, -38.920)	(-38.997, 5.250)	
Two-sided (95% CI)	(-71.269, -36.091)	(-43.238, 9.491)	
Difference in LS Means			
DexNP - Vehicle	-36.81		0.0115
Two-sided (70% CI)	(-53.576, -20.038)		
Two-sided (90% CI)	(-63.422, -10.191)		
Two-sided (95% CI)	(-68.524, -5.090)		
Student's two-sample T-test:			
Mean difference	-43.29		0.0064
Two-sided (70% CI)	(-61.321, -25.250)		
Two-sided (90% CI)	(-71.910, -14.660)		
Two-sided (95% CI)	(-77.396, -9.174)		

Safety Results

Summary of Treatment Emergent Adverse Events (Safety Population)

	DexNP Eye Drop (N=99)	Vehicle Eye Drop (N=45)
Number of TEAEs [1]	**134**	**50**
Number of subjects with TEAEs [2]	70 (70.7)	24 (53.3)
Number of serious TEAEs [1]	14	1
Number of subjects with serious TEAEs [2]	11 (11.1)	1 (2.2)
Number of related to the study medication TEAEs [1]	44	12
Number of subjects with related to the study medication TEAEs [2]	32 (32.3)	9 (20.0)
Number of severe TEAEs [1]	5	2
Number of subjects with severe TEAEs [2]	4 (4.0)	1 (2.2)
Number of TEAEs Leading to discontinuation from study medication [1]	5	0
Number of subjects with TEAEs leading to discontinuation from study medication [2]	5 (5.1)	0
Number of TEAEs leading to death [1]	2	0
Number of Subjects with AEs leading to death [2]	2 (2.0)	0

Abbreviation: TEAE=Treatment emergent adverse event
Only TAEs with date of first randomized study medication intake ≤ AE onset date ≤ date of completion/discontinuation are included;
[1] Number of events;
[2] Number and percentage of subjects.

Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	DexNP Eye Drop (N=99)		Vehicle Eye Drop (N=45)	
System Organ Class Preferred Term	**Number (%) of Subjects**	**Number of Events**	**Number (%) of Subjects**	**Number of Events**
At Least One TEAE	**70 (70.7)**	**134**	**24 (53.3)**	**50**
Eye disorders	33 (33.3)	42	15 (33.3)	26
Diabetic retinal edema	6 (6.1)	6	3 (6.7)	3
Eye irritation	3 (3.0)	3	0	0
Ocular hypertension	3 (3.0)	3	1 (2.2)	1
Visual acuity reduced	3 (3.0)	3	2 (4.4)	2
Cataract	2 (2.0)	2	1 (2.2)	1
Diabetic retinopathy	2 (2.0)	3	0	0
Visual acuity reduced transiently	2 (2.0)	2	0	0
Vitreous hemorrhage	2 (2.0)	2	0	0
Conjunctival hyperemia	0	0	2 (4.4)	2
Investigations	31 (31.3)	36	3 (6.7)	3
Intraocular pressure increased	24 (24.2)	26	0	0
Blood lactate dehydrogenase increased	2 (2.0)	2	0	0
Blood pressure increased	2 (2.0)	2	0	0
Infections and infestations	10 (10.1)	12	9 (20.0)	9
Influenza	4 (4.0)	4	3 (6.7)	3
Nasopharyngitis	4 (4.0)	4	3 (6.7)	3
Vascular disorders	6 (6.1)	6	2 (4.4)	2
Hypertension	3 (3.0)	3	2 (4.4)	2
Peripheral arterial occlusive disease	2 (2.0)	2	0	0
Cardiac disorders	5 (5.1)	5	1 (2.2)	2
Atrial fibrillation	2 (2.0)	2	0	0

Cardiac failure	2 (2.0)	2	1 (2.2)	1
Metabolism and nutrition disorders	4 (4.0)	5	1 (2.2)	2
Diabetes millitus	3 (3.0)	3	1 (2.2)	1
Musculoskeletal and connective tissue disorders	4 (4.0)	4	1 (2.2)	1
General disorders and administration site conditions	3 (3.0)	3	0	0
Nervous system disorders	3 (3.0)	3	0	0
Dysgeusia	3 (3.0)	3	0	0
Respiratory, thoracic and mediastinal disorders	4 (4.0)	4	0	0
Gastrointestinal disorders	3 (3.0)	4	0	0
Skin and subcutaneous tissue disorders	3 (3.0)	3	1 (2.2)	2
Blood and lymphatic system disorders	1 (1.0)	1	0	0
Ear and labyrinth disorders	1 (1.0)	1	0	0
Injury, poisoning and procedural complications	1 (1.0)	1	2 (4.4)	2
Psychiatric disorders	1 (1.0)	1	1 (2.2)	1
Renal and urinary disorders	1 (1.0)	2	0	0
Reproductive system and breast disorders	1 (1.0)	1	0	0
Surgical and medical procedures	1 (1.0)	1	3 (6.7)	3

Notes: TEAE = Treatment emergent adverse event;
Only adverse events with date of first randomized study medication intake ≤ AE onset date ≤ date of completion/discontinuation are included;
Table presents number, percentage of subjects and number of events with a cut-off of ≥2% TEAEs in any treatment group.

Other Relevant Findings

None

Date of Clinical Trial Report

27 March 2019