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Study ID: CMO-MA-EYE-0564

Title: Drug Utilization Study in Patients Receiving Ozurdex™ (Dexamethasone Intravitreal Implant) 0.7 mg Injections for Visual Impairment due to Diabetic Macular Edema (DME)

Statistical Analysis Plan Date: 24-Jul-2019

1.0 TITLE PAGE

Protocol N° CMO-MA-EYE-0564

Drug Utilization Study in Patients Receiving Ozurdex™ (Dexamethasone Intravitreal Implant) 0.7 mg Injections for Visual Impairment due to Diabetic Macular Edema (DME)

STATISTICAL ANALYSIS PLAN

Version 1.0: 24 JUL 2019

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AESI	adverse event of special interest
BCVA	best-corrected visual acuity
CI	confidence interval
eCRF	electronic case report form
EDC	electronic data capture
CNV	choroidal neovascularization
CRT	central retinal thickness
DME	diabetic macular edema
DV	derived variable
ETDRS	early treatment diabetic retinopathy study
IOP	intraocular pressure
OCT	optical coherence tomography
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
OU	oculus urteque (both eyes)
PT	preferred term
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
VEGF	vascular endothelial growth factor

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the real-world utilization, effectiveness and safety data as outlined in the final protocol of Study CMO-MA-EYE-0564 (version dated 24 JUL 2018). Specifications of tables, figures, and data listings are contained in a separate document.

Study design

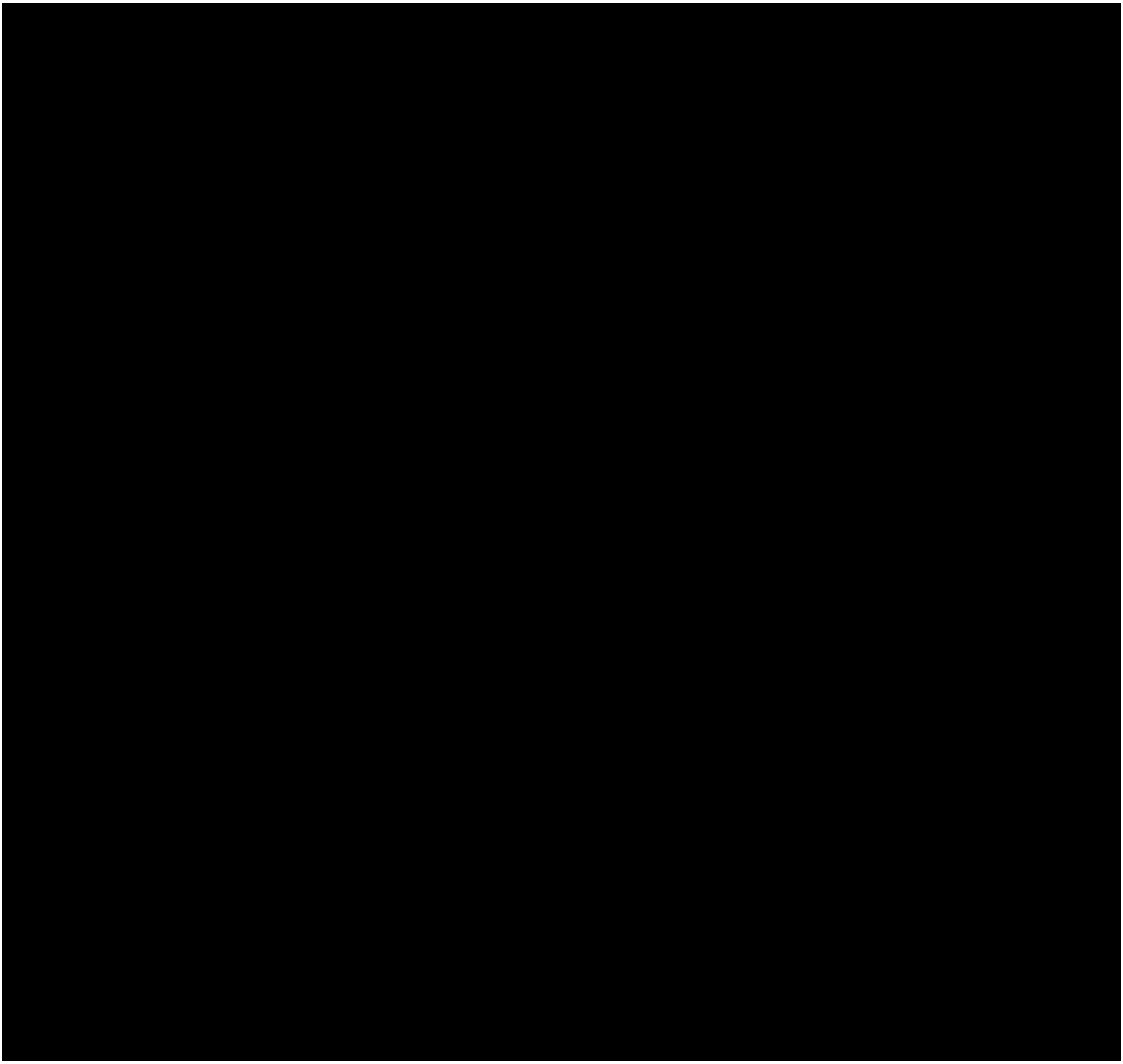
Study CMO-MA-EYE-0564 is a retrospective, non-interventional, observational, multi-center, drug utilization study to be conducted in adult patients with visual impairment due to DME treated with Ozurdex implants in Germany and Switzerland from 1 January 2015 to 1 September 2018. Data from approximately 150 patients will be collected by retrospective review of medical charts; including up to 50 patients that are naïve of any anti-VEGF treatment before their first Ozurdex implant injection. Sites will be hospital-based experienced medical retina centers treating DME patients.

Patients' medical charts will be selected over a 4-month period at each site or until the study target population has been reached. Site personnel will be invited to complete a screening log with all patients who received their first Ozurdex implant injection from 1 January 2015 until 1 September 2017 to help them identify eligible patients. For each patient, retrospective data on the study eye will be abstracted from existing medical records from time of first Ozurdex implant injection until 1 September 2018. Data abstraction will cover at least one year of follow-up after first Ozurdex injection for all selected patients. The study eye will be defined as the eye that received the most Ozurdex injections. Key relevant data will also be collected on the contralateral eye.

Consent from patients will not be requested; as the study is retrospective and anonymized, a waiver of consent will have been requested from the Ethics Committees.

Study assessments

The schedule of assessments for Study CMO-MA-EYE-0564 is presented in Table 4-1.



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Sites and study population

Site selection will aim to recruit qualified ophthalmologists experienced in intravitreal injections who are most likely to treat patients with DME with Ozurdex. A sample of ophthalmologists working in experienced medical retinal centers treating DME patients will thereby be selected.

From a public health and market access perspective, the present study population constitutes a broader real-world patient population than that reflected in clinical trials. The present study design cannot make any conclusions on causal relationships, but can rather explore real-world Ozurdex drug utilization patterns, effectiveness and safety. It is expected that the results from this study may be generalizable to the overall population presenting with DME and treated with Ozurdex in Germany and Switzerland.

Patients may contribute at most one eye into the study. If both eyes meet the inclusion and exclusion criteria, the eye that received the most Ozurdex injections will be chosen as the study eye.

Inclusion criteria are:

1. Patient received at least two Ozurdex implants in the study eye to treat visual impairment due to DME

2. Male or female patient aged ≥18 years at time of first Ozurdex implant injection in the study eye

3. First Ozurdex implant injection in the study eye occurred after 1 January 2015

4. Patient was followed-up at the site for at least 12 months after the first Ozurdex implant injection in the study eye

Exclusion criterion is:

1. Patient received Ozurdex implants in the study eye as part or during a clinical study

[redacted]

5.0 OBJECTIVES

Primary objective

The primary objective of this study is to assess reinjection interval of Ozurdex implants in patients with DME in real-world in Germany and Switzerland.

Secondary objectives

The secondary objectives of this study are:

- To assess the relationship between reinjection intervals and drug effectiveness
- To describe the reasons for reinjection
- To assess drug effectiveness in patients who are naïve of any anti-VEGF treatment
- To present those adverse events of special interest (AESIs) that may be potentially related to Ozurdex injection

6.0 PATIENT POPULATIONS AND SUBGROUPS

6.1 ELIGIBLE SCREENING LOG POPULATION

All patients from the screening log who meet selection criteria will be considered in the Eligible screening log population.

As a reminder, site personnel will be invited to complete a screening log with all patients who received at least one Ozurdex implant injection to help them identify eligible patients. Based on data recorded in the screening log, a patient will be considered as meeting selection criteria if s/he meets all the criteria below:

- The number of Ozurdex implant injections is ≥ 2 in at least one eye.
- Patient's age at first Ozurdex implant injection is ≥ 18 years old
- Date of the first Ozurdex implant injection is ≥ January 2015
- Time from the first Ozurdex implant injection to the most recent follow-up visit prior to 01 September 2018 [DV] is ≥ 365 days.
- 'Patient received Ozurdex implants as part or during a clinical trial' is equal to 'No'

6.2 ANALYSIS POPULATION

The Analysis population will consist of all selected patients for whom an eCRF have been completed and who meet selection criteria (See Section 4.0).

All analyses described in this SAP will be performed on the Analysis Population, unless otherwise specified.

6.3 SUBGROUPS

The following subgroups will be considered for analysis:

- Treated with Ozurdex in Switzerland vs. Germany
- Patients who are naïve of any anti-VEGF treatment in the study eye prior to the first Ozurdex injection in the study eye: Yes vs. No [DV].
- Number of anti-VEGF treatments in the study eye prior to the first Ozurdex injection in the study eye: 0, 1 to 3, 4 to 6, >6 [DV].
- Lens status of the study eye during the study period: Phakic throughout vs. Pseudophakic throughout vs. Change from Phakic to Pseudophakic [DV].

- At least one concomitant treatment with anti-VEGF and/or corticosteroids in the study eye: Yes vs. No [DV]

Table 6-1 presents subgroups that will apply for each analysis.

Table 6-1 Planned Subgroup Analyses

Analysis \ Subgroups	Treated with Ozurdex in Switzerland vs. Germany	Patient naïve to anti-VEGF in the study eye prior to the 1st Ozurdex injection in the study eye: Yes vs. No	Number of anti-VEGF treatments in the study eye prior to baseline: 0, 1 to 3, 4-6, >6	Lens status of the study eye during the study period: Phakic throughout vs. Pseudophakic throughout vs. Change from Phakic to Pseudophakic	At least one concomitant treatment with anti-VEGF and/or corticosteroids in the study eye: Yes vs. No
Demographics and other baseline characteristics (Section 10.0)	X				
Diabetes and DME status (Section 11.0)	X			X	
Clinical examination in the study eye (Section 12.0)	X				
Prior and concomitant treatments and surgeries (Section 13.0)	X				
Primary objective (Section 15.1)	X	X	X	X	X
First secondary objective (Section 15.2.1)	X	X	X	X	X
Second secondary objective (Section 15.2.2)	X	X	X		X
Third secondary objective (Section 15.2.3)					
Fourth secondary objective (Section 15.2.4)	X				

The planned subgroup analysis specified in Table 6-1 above may not be performed if the number of patients in the subgroup is too small.

7.0 BIAS AND LIMITATIONS

Selection bias is a potential limitation of the study, for both sites and patients. Sites will be selected from hospital-based experienced medical retina centers treating DME patients, as these centers will be experienced in intravitreal Ozurdex injections. Because the participating sites comprise a population of volunteers, non-response bias is possible.

In order to limited bias in the selection of patients, sites will attempt to consecutively select all patients who meet the selection criteria, regardless of demography or other considerations, based on the date of first Ozurdex implant injection. All patients meeting the selection criteria, regardless of their selection for the study, will be identifiable in a screening log collecting minimum non-identifying patient information (see Section 6.1). Characteristics of selected and non-selected patients will be compared to assess patient selection bias and reason for not being selected will be described (patient did not meet selection criteria, lack of time, quotes were met, etc.).

Information bias is a distortion in the estimate of association between risk factor and disease due to systematic measurement error or misclassification of patients on one or more variables, either risk factor or disease status. As the study is retrospective, it relies on data that have already been collected for another purpose (i.e. patient care). As a result, not all data to be collected in this study may be recorded in the medical charts, leading to a potential bias due to missing data. Moreover, as the study is anonymous, no queries will be issued to the sites in case of missing or incoherent data. Finally, as this is a multicenter study, the methods used to estimate the variables collected during the chart review process may be heterogeneous across sites. This has the potential to introduce systematic bias into the results.

Information bias is minimized by the use of EDC technology. In addition, to minimize the burden on investigators and sites, the EDC will maximize the quality and relevance of the data using automated online controls. To complement these automated online controls, principal investigators will be requested to review all entered data submitted in the EDC.

Confounding bias may result from selective prescribing of a particular treatment to more severely affected patients. As a result of higher background risk, reported event rates may be higher and give the appearance of an elevated risk related to the use of treatment. The collection of relevant medical information prior to first Ozurdex implant injection will help to identify the presence of elevated background risk of safety events, so that safety events can be compared through subgroup analysis to what was observed in available literature to determine whether the elevated risk is likely to be related to background risk (e.g. previous occurrence of glaucoma, previous cataract, previous anti-VEGF treatment) or use of Ozurdex.

8.0 PHYSICIAN AND PATIENT DISPOSITION

Physician disposition will be summarized overall and by country using descriptive statistics for the following parameters: number of solicited, responding, participating and active physicians, number of non-participating physicians and reason for non-participation, and number of patients included per physician. The number of physicians who returned the Screening logs will also be described.

Patient disposition will be summarized overall and by country using descriptive statistics for the following parameters: number of patients recorded in screening logs, number of patients in the Eligible screening log population and reason for exclusion, number of included patients, number and percentage of patients in the Analysis population and reason for exclusion, number of follow-up visits per patient, dates of the first and last date of the first Ozurdex injection in the study eye, date of the last follow-up visit and study duration (months) [DV] for patients from the Analysis population.

The proportion of patients from the Eligible screening log population actually included in the study will also be calculated using the variable *'Chart entered in EDC (Yes/No)'* from the Screening log. This proportion will enable to assess the representativeness of patients included in the study compared to patients not included.

9.0 DESCRIPTION OF THE ELIGIBLE SCREENING LOG POPULATION

Analysis will be performed overall and:

- by inclusion in the study (Yes vs. No). It is to be noted that due to patient anonymization it will not be possible to link patients listed in the screening log and patients included in the study; the number of patients included according to the screening log ('Chart entered to EDC=Yes') may not match with the number of patients actually included in the study according to eCRF. The variable 'Chart entered to EDC' from the screening log will be used to distinguish both of these groups.

- by reason for non-inclusion in the study (Did not meet selection criteria, Lack of time, Quotas were met, Other)

Characteristics of patients of the Eligible screening log population will be summarized using descriptive statistics for the following variables collected in the screening log: age at first Ozurdex implant injection (years), gender, anti-VEGF injections before the first Ozurdex implant injection (Yes, No), number of Ozurdex implant injections in each eye.

10.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

This section describes analyses that will be conducted on parameters that are collected at baseline only. Analyses of parameters that are collected at both baseline and during the follow-up (such as DME status or clinical examination in the study eye) have been considered in other sections (See sections 11.0, 12.0 and 13.0).

Demographics and other baseline characteristics will be summarized using descriptive statistics.

10.1 DEMOGRAPHICS

Demographic characteristics collected include gender, age at baseline (years) [DV], and study eye (OS, OD).

10.2 OPHTHALMIC HISTORY AND CURRENT OPHTHALMIC CONDITIONS

Ophthalmic conditions at baseline will be described by the following parameters:

- History of steroid response (Yes, No) and, if yes, specification of the eye (Study eye, Contralateral eye, Both eyes) [DV].
- Glaucoma (Yes, No) and, if yes: type (Controlled, Uncontrolled), primary or secondary glaucoma, specification of the eye (Study eye, Contralateral eye, Both eyes) [DV], time from onset of glaucoma to baseline (months) [DV], glaucoma treated with medication (Yes, No).
- Ocular hypertension (Yes, No) and, if yes: specification of the eye (Study eye, Contralateral eye, Both eyes) [DV], time from onset of ocular hypertension to baseline (months) [DV], ocular hypertension treated with medication (Yes, No).

10.3 MEDICAL HISTORY (OTHER THAN OPHTHALMIC)

Any relevant chronic medical condition and/or medical conditions in the study eye ongoing at baseline (Yes, No) will be summarized and medical history conditions and events will be described by SOC and PT (MedDRA version 21.1). If several conditions with the same SOC have been reported for the same patient, s/he will be counted once for that SOC. The same rule will apply for conditions presented per PT.

11.0 DIABETES AND DME STATUS

11.1 DIABETES AND HbA1c

Characteristics of diabetes summarized at baseline will include time from diabetes diagnosis to baseline (years) [DV] and type (type 1, type 2). HbA1c measured within 3 months before baseline will be described as a continuous parameter (in %) and as a categorical parameter (≤8%, >8%). The same parameters will be summarized for HbA1c at the last study visit.

11.2 DME STATUS

DME status at baseline and during the follow-up period will be analyzed using information collected in eCRF sections *'Demographics and DME History'* section of the eCRF (DM/F2 form) and *'DME Status'* (DMEF/F17 form).

DME status in the study eye at baseline will be summarized using the following parameters: time from DME diagnosis to baseline (months) [DV], time from onset of DME symptoms to baseline (months) [DV], severity of diabetic retinopathy (no apparent retinopathy, mild non-proliferative diabetic retinopathy, moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy), macular ischemia (Yes, No) and peripheral ischemia (Yes, No).

During the follow-up period, severity of diabetic retinopathy in the study eye will be summarized for each Ozurdex reinjection.

12.0 CLINICAL EXAMINATION IN THE STUDY EYE

Lens status, biomicroscopic and ophthalmoscopic examinations, and IOP in the study eye at baseline and during follow-up period will be summarized using descriptive statistics.

12.1 LENS STATUS

At baseline, lens status in the study eye will be first summarized by the number and percentage of patients in each category (Phakic, Pseudophakic, Aphakic). For pseudophakic patients, YAG capsulotomy (Yes, No) and anterior chamber lens (Yes, No) will be described. For phakic patients, nuclear opacity (Present, Absent), cortical opacity (Present, Absent), and posterior subcapsular opacity (Present, Absent) will be described. For each of the three parameters collected for phakic patients, grade (1, 2, 3) will be described.

The number and percentage of patients with a change in lens status from phakic to pseudophakic during follow-up will be summarized [DV]. Among patients with a change from phakic to pseudophakic during follow-up, opacities (nuclear opacity, cortical opacity, and posterior subcapsular opacity) and grade at baseline will be described. If a very small number of patients have a change in lens status, then the variable 'Type of change' will not be derived and the type of change will be described by a listing including raw data from eCRF section *'Biomicroscopy – Lens – Study eye'* (BIL/F8 form) at baseline and at follow-up visits a change has been reported.

A subgroup of patients will be identified by lens status during the study period: phakic throughout vs. pseudophakic throughout vs. change from phakic to pseudophakic [DV].

12.2 BIOMICROSCOPY

At baseline, the number and percentage of patients with biomicroscopy data available for the study eye will be described. Then, for patients with data available, the following parameters will be described:

- Any adverse findings (Yes, No)

- Conjunctiva (bulbar or palpebral): hyperemia (Normal, Trace +0.5, Mild +1, Moderate +2, Severe +3), edema (Normal, Trace +0.5, Mild +1, Moderate +2, Severe +3), subconjunctival hemorrhage (Normal, Trace +0.5, Mild +1, Moderate +2, Severe +3). Adverse findings will also be described as 'Absent vs. Present' [DV].

- Cornea: edema (Normal, Trace +0.5, Mild +1, Moderate +2, Severe +3), superficial punctate keratopathy (Normal, Trace +0.5, Mild +1, Moderate +2, Severe +3). Adverse findings will also be described as 'Absent vs. Present' [DV].

- Anterior chamber: cells (Normal, +0.5, +1, +2, +3, +4), flare (Normal, Faint +1, Moderate +2, Marked +3, Intense +4), hypopyon (Present, Absent) and, if present, level in mm. Findings on cells and flare will also be described as 'Absent vs. Present' [DV].

- Iris/Pupil: pathology (Present, Absent), peripheral iridotomy noted (Yes, No), rubeosis iridis (according to categories 'Normal, +0.5, +1, +2, +3'). Adverse findings will also be described as 'Absent vs. Present' [DV]. Pathologies will be described by PT (MedDRA version 21.1). If more than one pathology with the same PT have been reported for the same patient, s/he will be counted once for that PT.

During the follow-up period, the number and percentage of patients having at least one adverse finding in the study eye (Yes, No) [DV] will be described. Then, for all patients with at least one adverse finding, the type of adverse finding will be described as 'Present, absent' for each pre-listed category: conjunctiva (hyperemia, Edema, subconjunctival hemorrhage), cornea (edema, superficial punctate keratopathy), anterior chamber (cells, flare, hypopyon) and iris/pupil (pathology, peripheral iridotomy, rubeosis iridis). If an adverse finding has been reported more than once for the same category for the same patient, s/he will be counted once for that category. For patients with at least one adverse finding during the follow-up period, a listing will also be presented with all biomicroscopy results at baseline and during the follow-up period.

12.3 OPHTHALMOSCOPIC EXAMINATION

At baseline, the number and percentage of patients with ophthalmoscopic data available for the study eye will be described. Then, for patients with data available, the following parameters will be summarized using descriptive statistics:

- Any adverse findings (Yes, No)

- Macula pathology: edema (Present, Absent), hemorrhage (Present, Absent), exudate (Present, Absent), macular scarring (Present, Absent), drusen (Present, Absent), Choroidal neovascularization (CNV) (Present, Absent), cup to disc ratio.

- Vitreous: cells (Normal, +0.5, +1, +2, +3, +4), haze (Normal, +0.5, +1, +2, +3, +4), hemorrhage (Normal, +0.5, +1, +2, +3, +4), posterior detachment (Present, Absent). Findings on cells, haze and hemorrhage will also be described as 'Absent vs. Present' [DV].

- Peripheral retina: hemorrhage (Present, Absent), tear/holes (Present, Absent), laser treatment (Yes, No)

- Other macula pathology and peripheral retina findings will be described by PT (MedDRA version 21.1). If several pathologies/findings with the same PT are reported for the same patient, s/he will be counted once for that PT.

During the follow-up period, the number and percentage of patients having at least one adverse finding in the study eye (Yes, No) [DV] will be described. Then, for all patients with at least one adverse finding, the type of adverse finding will be described as 'Present, absent' for each pre-listed category (macula pathology (edema, hemorrhage, exudate, etc), vitreous (cells, haze, etc), peripheral retina (hemorrhage, tear/holes, etc)) as well as for adverse findings reported as other macula pathology and peripheral retina. If an adverse finding has been identified more than once for the same category for the same patient, s/he will be counted once for that category. For patients with at least one adverse finding during the follow-up period, a listing will also be presented with results of ophthalmoscopic examination at baseline and during the follow-up period.

12.4 IOP

IOP (mmHg) in the study eye will be summarized at baseline using descriptive statistics.

IOP (mmHg) measured at 7-12 weeks after the first Ozurdex injection in the study eye, as well as at 7-12 weeks after each reinjection in the study eye, will be described using descriptive statistics. A figure will be presented for the mean IOP (mmHg) with 95% CIs at baseline, at each Ozurdex reinjection, and at 7-12 weeks after each Ozurdex injection in the study eye. In addition, the change in IOP (mmHg) from baseline to 7-12 weeks following each Ozurdex injection [DV], and the change from each Ozurdex reinjection to 7-12 weeks following reinjection [DV] will be described using descriptive statistics.

The following rules will apply for this description:

- IOP assessed on or after the day of subsequent injections (injection 2, injection 3, etc) will be included in this description.

- If there is more than one IOP measurement within the 7-12 week time window, the mean value will be considered for the description (See rule defined in section 21.2).

- If an Ozurdex injection is performed in the study eye at a follow-up visit, then investigators are asked to report in the EDC the IOP measured before the injection. This value will be considered for analysis.

13.0 PRIOR AND CONCOMITANT TREATMENTS AND SURGERIES

Prior medication/surgery is defined as any medication/surgery taken before the date of the first Ozurdex injection in the study eye. Concomitant medication/surgery is defined as any medication/surgery taken on or after the date of the first injection in the study eye.

13.1 ANTI-VEGF AND CORTICOSTEROID TREATMENTS

Prior medications

Prior treatments with anti-VEGF and corticosteroids in the study eye will be summarized using descriptive statistics for the following parameters: any anti-VEGF or corticosteroids treatment (Yes, No), at least one anti-VEGF treatment (Yes, No) [DV] and number of treatments [DV], at least one corticosteroid (Yes, No) [DV] and number of treatments [DV]. Then, each anti-VEGF treatment pre-listed in the eCRF (Avastin®, Lucentis®, Eylea® and Macugen®) and each corticosteroid treatment pre-listed (Triamcinolone®, Iluvien®) will be summarized by the number and percentage of patients treated and the number of treatments received per patient. The number and percentage of patients treated with at least one treatment of the category 'Other anti-VEGF therapy' will be described and treatments reported within this category will be described by generic name (WhoDrug B3 format version 01SEP2018). The same will be done for treatments reported in the category 'Other corticosteroid therapy'.

The time from the last anti-VEGF treatment to baseline (months) [DV], the time from the last corticosteroid treatment to baseline (months) [DV] and the time from the last treatment (the last among anti-VEGF and corticosteroids) to baseline (months) [DV] will be described using descriptive statistics.

Concomitant medications

Concomitant anti-VEGF and corticosteroid treatments will be summarized using the same methodology as for prior medications (see above) except for times from last treatment to baseline that are not applicable for concomitant treatments. The time from baseline to first anti-VEGF treatment (months) [DV] and time from baseline to first corticosteroid treatment (months) [DV] will be described using descriptive statistics, as well as the time from each Ozurdex reinjection to first receipt of anti-VEGF treatment (months) [DV] and corticosteroids treatment (months) [DV], respectively.

13.2 CONCOMITANT IOP-LOWERING MEDICATIONS

Concomitant IOP-lowering medications in the study eye will be summarized using descriptive statistics for the following parameters: at least one IOP-lowering medication (Yes, No) [DV] and description of IOP-lowering medication by generic name (WhoDrug B3 format version 01SEP2018). The time from baseline to first IOP-lowering medication (months) [DV] and time from each Ozurdex reinjection to first receipt of IOP-lowering medication (months) [DV] will be described using descriptive statistics.

13.3 OTHER CONCOMITANT OPHTHALMIC MEDICATIONS

Concomitant ophthalmic medications other than anti-VEGF, corticosteroids and IOP-lowering medications will be summarized using descriptive statistics for the following parameters: at least one other medication in the study eye (Yes, No) [DV], at least one other systemic medication (Yes, No) [DV], Medications will be described by generic name (WhoDrug B3 format version 01SEP2018) separately for medications in the study eye and medications for other medical conditions.

13.4 CATARACT AND GLAUCOMA PROCEDURES IN THE STUDY EYE

Prior procedures

Ocular surgical history and treatment history in the study eye prior to the first Ozurdex injection on the study eye will be summarized using descriptive statistics for the following parameters:

- Glaucoma related interventions: glaucoma laser (Yes, No), trabeculectomy (Yes, No), glaucoma valve implant (Yes, No) and laser peripheral iridotomy (Yes, No)

- Retinal lasers: focal retinal laser (Yes, No), PRP retinal laser (Yes, No). The number of treatments per patient and the time from the last treatment to baseline (months) [DV] will also be summarized for focal and PRP retinal laser separately.

- Retinal surgeries: pars plana vitrectomy (Yes, No) and, if yes, description of the number of treatments per patient and of the time from the last treatment to baseline (months) [DV].

- Other treatments/interventions: any treatment (Yes, No) and description of treatments reported by PT (MedDRA version 21.1). If several treatments with the same PT are reported for the same patient, the patient will be counted once for that PT.

Concomitant procedures

Any concomitant ocular surgeries in the study eye (Yes, No), cataract surgery, each glaucoma intervention (Glaucoma surgery, glaucoma laser, trabeculectomy, glaucoma valve implant, laser peripheral iridotomy) and retinal related surgery (pars plana vitrectomy) will be summarized using descriptive statistics. Time from baseline to first surgical procedure (months) [DV] will be presented for each procedure.

Retinal related laser procedures (focal retinal laser; PRP retinal laser) will be summarized as above; however, these laser procedures also will be described by intervals after each Ozurdex reinjection during follow-up. Specifically, time from each Ozurdex reinjection to the first retinal laser procedure (months) will be summarized in addition to time from baseline to retinal laser procedure (months) [DV].

Other procedures reported in the 'Other' category will be summarized by PT (MedDRA version 21.1). If several procedures/treatments with the same PT are reported for the same patient, the patient will be counted once for that PT.

14.0 EXTENT OF EXPOSURE

The description of Ozurdex implant injections received by patients (number and reinjection interval) is covered in Section 15.1.

15.0 ANALYSES OF THE OBJECTIVES OF THE STUDY

15.1 ANALYSIS OF THE PRIMARY OBJECTIVE

The primary objective *'To assess reinjection interval of Ozurdex implants in patients with DME in real-world in Germany and Switzerland'* will be assessed by the following outcomes:

- Total number of Ozurdex reinjections in the study eye during follow-up, and considering years after the first Ozurdex injection in the study eye (See definition in Table 21-1).

- Reinjection interval defined in months as: (Date of injection (j+1) – Date of injection j) ÷ (365.25÷12), for j=1,…,n where n is the number of reinjections in the study eye. The result will be rounded to 0.1.

The number of Ozurdex reinjections in the study eye per year will be first summarized using descriptive statistics for the following parameters:

- The total number and percentage of Ozurdex reinjections received during follow-up.

- Number and percentage (with 95% CI) of patients with at least one Ozurdex reinjection during Year 1 (See definition in Table 21-1), and number of reinjections per patient during Year 1, for all patients in the analysis population. Note: the first Ozurdex injection will not be considered here, only reinjections will be counted.

- Number and percentage (with 95% CI) of patients with at least one Ozurdex reinjection and number of reinjections per patient during Year k (k=2, 3), for patients having a complete Year k of follow-up (see definition of 'Complete year' in Section 21.2).

- Number and percentage of patients receiving each Ozurdex reinjection (first, second, third, etc) for each year of follow-up (Year k, k=1 to 3) considering patients having the complete year of follow-up.

The Ozurdex reinjection interval in the study eye will be described using descriptive statistics for the following parameters:

- Reinjection interval (months) considering all eligible reinjections recorded in the EDC. The 95% CI of the mean will also be presented.

- Reinjection interval (months) considering each reinjection separately (i.e. first reinjection, second reinjection, etc). 95% CI of the mean will also be presented.

15.2 ANALYSIS OF THE SECONDARY OBJECTIVES

15.2.1 First Secondary Objective

The secondary objective *'To assess the relationship between reinjection intervals and drug effectiveness'* will be assessed considering the following outcomes:

- Reinjection interval in months defined for each reinjection in the study eye (see definition in Section 15.1)
- For effectiveness (in the study eye):
    - BCVA change (ETDRS letters) from the last assessment prior to Ozurdex injection to 7–12 weeks following each Ozurdex implant injection
    - BCVA change (ETDRS letters) from the last assessment prior to the first Ozurdex implant injection to 7-12 weeks following each Ozurdex implant injection
    - CRT by OCT change (µm) from the last assessment prior to Ozurdex injection to 7-12 weeks following each Ozurdex implant injection
    - CRT by OCT change (µm) from the last assessment prior to the first Ozurdex implant injection to 7-12 weeks following each Ozurdex implant injection

Description of drug effectiveness in the study eye

As preliminary description of drug effectiveness, BCVA in the study eye will be described at baseline and during the follow-up period using descriptive statistics for the following parameters:

- Last BCVA (ETDRS letters) prior to each Ozurdex injection [DV]
- BCVA (ETDRS letters) at 7-12 weeks following each Ozurdex injection,
- Change in BCVA (ETDRS letters) from baseline to 7-12 weeks following each Ozurdex injection [DV],
- Change in BCVA (ETDRS letters) from the value prior to Ozurdex reinjection to 7-12 weeks following each Ozurdex reinjection [DV].

Note: See the rule defined in Section 21.2 in case several measurements are available within the 7-12 week time window.

A similar description will be performed for CRT (µm) in the study eye, regardless of the technology used for CRT measurement (confocal scanning laser ophthalmoscope; OCT; OCT – angiography; retinal thickness analyser; ultrasound).

Relationship between reinjection interval and drug effectiveness

The potential relationship between Ozurdex reinjection interval and BCVA will be assessed by considering, for each Ozurdex injection j (j≥1) in the study eye, the time interval between injection j and injection (j+1) and BCVA change from the value prior to injection (j+1) to 7-12 weeks following injection (j+1). All injections of the patient will be considered all together for this analysis.

As a first approach, a figure (scatter plot) defined by Ozurdex reinjection interval (in months) on the horizontal axis and BCVA change (in ETDRS letters) on the vertical axis will be plotted. A linear regression line along with the spearman rank coefficient and p-value will be superimposed on the data of the scatter plot.

As a second approach, the median Ozurdex reinjection interval will be calculated considering all reinjection intervals for a patient. BCVA change (in ETDRS letters) will be then summarized using descriptive statistics by reinjection intervals categorized in two classes according to the median (≤ median; > median). The 95% CI of the mean BCVA change will be provided in each class. Based on the observed distribution, other categories than the median may be considered to categorize the reinjection interval.

The same analysis will be performed considering, for each Ozurdex injection j (j≥2) in the study eye, the time interval between injection j and injection (j+1) and BCVA change from the value prior to the first Ozurdex injection in the study eye (=baseline value) to 7-12 weeks following injection (j+1).

A similar analysis will be performed to assess the potential relationship between reinjection interval and CRT in the study eye.

15.2.2 Second Secondary Objective

The secondary objective *'To describe the reasons for reinjection'* will be assessed considering the primary reason for injection (Disease progression, Lack of effect, Other) reported at each follow-up visit at which an Ozurdex injection was performed in the study eye. The analysis will be summarized using descriptive statistics.

For the study eye, the primary reason for injection (Disease progression, Lack of effect, Other) will be first summarized for each reinjection (i.e. first reinjection, second reinjection, etc.). Then, the primary reason for injection will be described considering all reinjections (the denominator for percentages will be the total number of reinjections in the study eye). Reasons reported as free texts in the 'Other' category will be summarized in a listing.

15.2.3 Third Secondary Objective

The secondary objective *'To assess drug effectiveness in patients who are naïve of any anti-VEGF treatment'* will be assessed by carrying out analyses detailed in the paragraph *'Description of drug effectiveness'* in Section 15.2.1 in the subgroup of patients who are naïve of any anti-VEGF treatment in the study eye prior to the first Ozurdex injection in the study eye vs. patients who received at least one anti-VEGF treatment in the study eye prior to the first Ozurdex injection in the study eye. Comparison between both subgroups will be purely descriptive (no statistical tests will be computed).

In addition, a subgroup of patients will be identified by the number of anti-VEGF treatments in the study eye prior to the first Ozurdex injection in the study eye. The number of treatments will be categorized: 0, 1 to 3, 4 to 6, >6 [DV].

15.2.4 Fourth Secondary Objective

The secondary objective *'To present those AESIs that may be potentially related to Ozurdex reinjection'* will be assessed by the presence of the following AESIs:

- Cataract or lens opacities
- Glaucoma
- Hypotony
- Implant dislocation
- Infection vs. Non-infection related ocular inflammation
- Intraocular hypertension
- Mechanical failure of device and implant misplacement
- Ocular bleeding or hemorrhage
- Retinal detachment (tear or hole)
- Significant vitreous loss
- Vitreous detachment

These AESIs will be identified from eCRF section *'Adverse events'* (AE/F20 form) in which they are pre-listed.

All AESIs that began on or after the date of the first Ozurdex injection in the study eye will be considered for analysis. The analysis will be performed:

- considering all AESIs, AESIs that occur in the study eye, and AESIs that occur in the contralateral eye.

- cumulatively considering all AESIs and broken down by the number of injections, i.e. considering AESIs that occur after the first Ozurdex injection at baseline, AESIs that occur after the first Ozurdex reinjection, AESIs that occur after the second Ozurdex reinjection, etc. AESIs that occur on the same day of an Ozurdex injection will be considered as occurring after the injection.

AESIs will be summarized using descriptive statistics for the following parameters:

- Number and percentage (with 95% CI) of patients who experienced at least one AESI.

[redacted]

16.0 SAFETY ANALYSES

Safety analysis is covered by the analysis of the secondary objective *'To present those AESIs that may be potentially related to Ozurdex* reinjection' (see Section 15.2.4).

17.0 OFF-LABEL USE OF OZURDEX

Off-label uses of Ozurdex will be identified from eCRF section *'Adverse events'* (AE/F20 form) and will be summarized by: number and percentage of patients with at least one off-label use of Ozurdex, and reason that caused Ozurdex use to be off-label (free text will be reported).

18.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

19.0 DETERMINATION OF SAMPLE SIZE

The study aims to select 150 patients. As study primary objective is to assess reinjection interval of Ozurdex implant in real-world, sample size calculations were performed to evaluate the precision around the mean of the reinjection interval.

Few data were published on the reinjection interval in patients diagnosed with DME in real-world. Matropasqua et al. reported a mean ± standard deviation (SD) of 6.7±2.3 months in 27 Italian patients. Querques et al. reported a mean of 4.9 and 4.7 months from respectively 570 French patients of a pharmacist database and 114 patients from the French Social Security database (no standard deviations were available). The same study also reported a mean (±SD) of 4.8±1.8 months between reinjections based on data from 111 French ophthalmologists who completed a survey about their practice.

The precision of the 95% CI of the mean (ω, half of the width of the CI) is determined using the following formula:

$\omega = \frac{1.96 \times SD}{\sqrt{n}}$, where SD is the standard deviation and n is the sample size.

Table 18-1 shows the precision and 95% CI of the mean considering a SD ranging from 1.5 to 3.0 and a sample size of 150 patients.

Table 18-1 Precision (ω) and 95% CI of the mean considering a standard deviation ranging from 1.5 to 3.0, a mean ranging from 4.7 to 6.7 and a sample size of 150 patients

SD	Mean (months)				
	ω	**4.7**	**5.5**	**6.0**	**6.7**
1.5	0.2	4.5-4.9	5.3-5.7	5.8-6.2	6.5-6.9
2.0	0.3	4.4-5.0	5.2-5.8	5.7-6.3	6.4-7.0
2.5	0.4	4.3-5.1	5.1-5.9	5.6-6.4	6.3-7.1
3.0	0.5	4.2-5.2	5.0-6.0	5.5-6.5	6.2-7.2

Considering SD of the mean reinjection interval ranging from 1.5 to 3 months, the selection of 150 patients will enable the description of a mean reinjection interval with precision ranging from 0.2 to 0.5 months, i.e. from 6 to 15 days (worst case).

For example, for a mean interval between two Ozurdex injections of 6.0 months, the 95% CI of the mean would be 6.0 [5.5-6.5] months in the worst case (i.e., 183 days [168-198], ω =15 days).

A secondary objective of the study is to assess drug effectiveness in a subgroup of patients who are naïve of any anti-VEGF treatment. One of the outcomes of interest for this subgroup of patients will be the change in BCVA from the first injection to 7-12 weeks following each reinjection.

In 2015 Escobar-Barranco et al. reported a difference in visual acuity from baseline to 6 months (mean ± SD) of 11.5±4.6 ETDRS letters in 36 treatment naïve patients whereas in 2018 Iglicki et al. reported a gain at 24 months (mean ± SD) of 11.3±10.0 letters in 71 eyes of treatment naïve patients.

The precision and 95% CI of the mean have been calculated considering a mean gain of 11.5 letters, a standard deviation ranging from 4.5 to 10.0 and a sample size of 50 patients (Table 18-2).

Table 18-2 Precision (ω) and 95% CI of the mean considering a mean gain of 11.5 letters, a standard deviation ranging from 4.5 to 10.0 and a sample size of 50 patients

SD	ω	95% CI
4.5	1.3	10.2-12.8
6.0	1.7	9.8-13.2
8.0	2.2	9.3-13.7
10.0	2.8	8.7-14.3

Considering SD ranging from 4.5 to 10.0, a subgroup of 50 patients who are treatment naïve will enable to describe a mean change in visual acuity with precision ranging from 1.3 to 2.8. For example, for a mean change in visual acuity of 11.5 letters, the 95% CI of the mean will be 11.5 [8.7-14.3] letters in the worst case. It has been considered as satisfactory for this secondary objective.

20.0 STATISTICAL SOFTWARE

Statistical analyses will be performed [redacted]. Analysis datasets will be created from the raw EDC datasets to facilitate programming of Tables, Figures, and Listings (TFL). Proposed shells for TFLs will be provided in Microsoft Word format.

21.0 DATA HANDLING CONVENTIONS

21.1 STATISTICAL RULES AND DATA FORMATS

Continuous variables

Continuous (quantitative) variables will be described by the number of non-missing and missing observations, mean, SD, median, first and third quartiles and extreme values (minimum and maximum). The following rules will be applied:

- If the raw/derived variable is an integer, then mean, median, SD, first and third quartiles will be rounded to one decimal.
- If the raw/derived variable is a decimal number, then mean, median, SD, first and third quartiles will be reported using the same number of decimal places as the raw/derived data.
- Minimums and maximums will be reported with the same number of decimals with which the raw/derived variable is recorded/calculated.
- If the standard deviation is not computable, then it will be displayed as 'NA' (Not applicable).

Categorical variables

Categorical (qualitative) variables will be described by the observed and relative (%) frequency of each class, and number of non-missing and missing observations. Unless otherwise specified, missing data will not be included in the denominator for the calculation of percentages. If necessary, the denominator will be specified in a footnote to the tables for clarification. Multiple answers will also be specified, where applicable.

If 'Not in chart' or 'unknown' is a class of response, then it will be considered as missing for analysis.

Percentages will be rounded to one decimal place, except for the following specific cases:

- If the percentage is equal to 0, then a blank will be left instead of "0.0%"
- If the percentage is <0.1, then "<0.1%" will be used
- If the percentage is equal to 100, then "100%" will be used, i.e. no decimal place will be displayed
- If the percentage is >99.9, then ">99.9%" will be used.

Confidence intervals

Confidence intervals for means and exact confidence intervals (Clopper-Pearson) for percentages will be calculated when appropriate and will be 2-sided at the 95% level.

Figures

Figures will be performed when appropriate. In particular, the relationship between two continuous variables will be assessed using a scatter plot: one continuous variable will be plotted on the horizontal axis and the other continuous variable will be plotted on the vertical axis.

21.2 STUDY PERIODS

Baseline

The baseline is defined as the day of the first Ozurdex implant injection in the study eye.

The baseline time period is defined as the 3-month period prior to the first Ozurdex injection in the study eye. This 3-month period prior to first Ozurdex injection in the study eye applies to assessments of prior ocular surgical history and treatments, IOP, BCVA, and CRT measures.

Follow-up period

The period starting the day after the day of the first Ozurdex injection in the study eye is the follow-up period (= post-baseline period). End of follow-up occurs at the last study visit or first receipt of concomitant treatment with anti-VEGF and/or corticosteroids, whichever comes first.

Years after the first Ozurdex injection in the study eye

Years after the first Ozurdex injection in the study eye will be defined as per Table 21-1 below. A patient will be considered to have a complete Year Y of follow-up if the time from the first Ozurdex injection in the study eye to the last follow-up visit is greater or equal to the upper bound of Year Y.

Table 21-1 Definition of years after the first Ozurdex injection in the Study eye

Year #[a]	Year definition[b]
Year 1	Days [2, 365]
Year 2	Days [366, 731]
Year 3	Days [732, 1096]

[a] As per protocol all patients will have at least 1 complete year of follow-up at the site and the maximum number of complete years will be 3. The 1st Ozurdex injection should occur after 1 January 2015 and data will be collected up to 1 September 2018.

[b] Relative to the date of the first Ozurdex injection in the study eye. Day 1 = the date of the first Ozurdex injection in the study eye. There is no Day 0.

Time window (in weeks) after each Ozurdex injection in the study eye

For each Ozurdex injection in the study eye, follow-up visits performed at 7-12 weeks (+/- 2 weeks) (Days [35, 98]) after injection will be described. The time window of 7-12 weeks is relative to the date of each Ozurdex injection in the study eye, where Day 1 = date of the injection (there is no Day 0).

For IOP, BCVA and CRT, which are collected at follow-up visits, the date of assessment is the date of the follow-up visit at which they are reported. Therefore, for each Ozurdex injection, these parameters will be described at the date of assessment and 7-12 weeks after injection. If there is more than one assessment within the 7-12 week time window, then the mean value will be used for analysis considering IOP in mmHg, BCVA in approximate ETDRS letters, and CRT in µm.

For HbA1c, the date of assessment is collected at follow-up visits. However, assessment of HbA1c will be presented only at baseline and last study visit.

21.3 DERIVED VARIABLES

Derivation details of all variables that will be derived in analysis datasets are defined in this section. Derived variables are identified in square brackets ([DV]) in the other sections of the SAP.

21.3.1 Variables related to Anti-VEGF and Corticosteroids Treatments

Identification of anti-VEGF and Corticosteroids treatments

Prior and concomitant anti-VEGF and Corticosteroids treatments will be identified from treatments reported in the following sections of the eCRF: *'Prior intravitreal injections/Corticosteroids in Study eye'* (PII/F6 form), and *'Concomitant Medications (inclusive of intravitreal injections, systemic Steroids, and IOP medications)'* (CM/F18 form).

In these sections, anti-VEGF treatments will be identified as:

- pre-listed treatments: Avastin®, Lucentis®, Eylea® and Macugen®,
- treatments reported in the category 'Other anti-VEGF therapy'

and corticosteroids will be identified as:

- pre-listed treatments: Triamcinolone® and Iluvien®,
- treatments reported in the category 'Other corticosteroid therapy'.

Number of anti-VEGF treatments in the study eye prior to the first Ozurdex implant injection in the study eye

The variable will be derived from information collected in eCRF section *'Prior intravitreal injections/Corticosteroids in Study eye'* (PII/F6 form).

The variable will be first derived as continuous variable to:

- 0,
    - if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is equal to 'No',
    - or if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is ticked to 'Yes', no anti-VEGF treatments are reported and at least one corticosteroid treatment is reported.
- the sum of the numbers of treatments reported for anti-VEGF treatments, if at least one anti-VEGF treatment is reported.

- missing,
    - if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is missing
    - or if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is equal to 'Yes' and no treatments have been reported in the table (neither anti-VEGF nor corticosteroids treatments)
    - or if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is equal to 'Yes' and at least one anti-VEGF treatment is reported with the corresponding number of treatments that is missing.

The continuous variable will be then categorized in the following categories: 0, 1 to 3, 4 to 6, and >6.

Number of corticosteroid treatments in the study eye prior to the first Ozurdex implant injection in the study eye

This variable will be derived in the same way that the variable 'Number of anti-VEGF treatments in the study eye prior to the first Ozurdex implant injection in the study eye' (See definition above) using information from appropriate sections of the eCRF.

At least one anti-VEGF treatment in the study eye before the first Ozurdex injection in the study eye (Yes, No)

The variable will be derived using information reported in eCRF section *'Prior intravitreal injections/Corticosteroids in Study eye'* (PII/F6 form). The variable will be derived to:

- Yes, if at least one anti-VEGF treatment is reported (= check box ticked)
- No,
    - if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is equal to 'No',

- or if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is ticked to 'Yes', no anti-VEGF treatments are reported and at least one corticosteroid treatment is reported.

- Missing,
  - if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is missing
  - or if the variable *'1.0.1 - Prior to first Ozurdex injection in the study eye for DME, did the patient receive any anti-VEGF or Corticosteroid therapy to treat the study eye?'* is equal to 'Yes' and no treatments have been reported in the table (neither anti-VEGF nor corticosteroids treatments)

<u>At least one corticosteroid therapy in the study eye prior to the first Ozurdex implant injection in the study eye (Yes, No).</u>

This variable will be derived in the same way that the variable *'At least one anti-VEGF treatment prior to the first Ozurdex implant injection in the study eye'* (See definition above).

<u>At least one concomitant anti-VEGF treatment in the study eye (Yes, No)</u>

The variable will be derived using the date of the first Ozurdex injection in the study eye (eCRF section *'Inclusion and Exclusion Criteria'* (IE/F1 form)), the side of the study eye (OS/OD, eCRF section *'Demographics and DME history'* (DM/F2 form)) as well as information reported in eCRF section *'Concomitant Medications (inclusive of intravitreal injections, systemic Steroids, and IOP medications)'* (CM/F18 form). The variable will be derived to:

- Yes, if at least one anti-VEGF treatment is reported with *'1.6.1 - Specify eye'* = {the side of the study eye, 'OU'}

- No,
  - If the variable *'1.1 - Were any ophthalmic concomitant medications taken (including intravitreal injections, systemic steroids, and IOP medications)?'* is equal to 'No'

- Or, if the variable *'1.1 - Were any ophthalmic concomitant medications taken (including intravitreal injections, systemic steroids, and IOP medications)?'* is equal to 'Yes' and no anti-VEGF treatments are reported

- Or, anti-VEGF treatment(s) are reported however for all anti-VEGF treatments *'1.6.1 - Specify eye'* is equal to the side of the contralateral eye

- Missing,

  - If the variable *'1.1 - Were any Ophthalmic Concomitant Medications taken (including Intravitreal injections, systemic Steroids, and IOP medications)?'* is missing

  - Or, if the variable *'1.1 - Were any Ophthalmic Concomitant Medications taken (including Intravitreal injections, systemic Steroids, and IOP medications)?'* is equal to 'Yes' however no medications have been reported in the form

  - Or, if at least one anti-VEGF treatment is reported with *'1.6.1 - Specify eye'* that is missing and there is no anti-VEGF treatment reported with *'1.6.1 - Specify eye'* = {the side of the study eye, 'OU '}.

<u>At least one concomitant corticosteroid therapy in the study eye (Yes, No)</u>

This variable will be derived in the same way that the variable '*At least one concomitant anti-VEGF treatment in the study eye'* (See definition above).

At least one concomitant anti-VEGF or corticosteroid therapy in the study eye (Yes, No)

The variable will be defined from the 2 derived variables '*At least one concomitant anti-VEGF treatment in the study eye'* and '*At least one concomitant corticosteroid therapy in the study eye'*. It will be derived to:

- Yes, if '*At least one concomitant anti-VEGF treatment in the study eye'* and/or '*At least one concomitant corticosteroid therapy in the study eye'* is equal to 'Yes'.

- No, if '*At least one concomitant anti-VEGF treatment in the study eye'* and '*At least one concomitant corticosteroid therapy in the study eye'* are both equal to 'No'.

- Missing, if '*At least one concomitant anti-VEGF treatment in the study eye'* and/or '*At least one concomitant corticosteroid therapy in the study eye'* is missing and none of them are equal to 'Yes'.

21.3.2 Variables Related to IOP-Lowering Medications and Other Ophthalmic Concomitant Medications

Identification of concomitant IOP-lowering medications

Concomitant IOP-lowering medications will be identified from treatments reported in eCRF section *'Concomitant Medications (inclusive of intravitreal injections, systemic Steroids, and IOP medications)'* (CM/F18 form) as:

- pre-listed treatments: Acetazolamide, Apraclonidine, Bimatoprost, Brimonidine, Brinzolamide, Carbachol, Carteolol, Clonidine, Dorzolamide, Latanoprost, Levobunolol, Pilocarpine.

- treatments reported in the category 'Other': IOP-lowering medications will be identified by an exhaustive review of treatments reported in this category: Tafluprost, Timolol maleate, Travoprost, Bimatoprost, Timolol maleate, Brimonidine; Brinzolamide, Brimonidine; Timolol maleate, Brinzolamide;Timolol maleate, Dorzolamide; Timolol maleate, Latanoprost; Timolol maleate, Travoprost; Timolol maleate

At least one concomitant IOP-lowering medication in the study eye (Yes, No)

This variable will be derived in the same way as the variable *'At least one concomitant anti-VEGF treatment in the study eye (Yes vs. No)'* (See Section 20.3.1).

Identification of other concomitant ophthalmic medications

Other concomitant ophthalmic medications will be identified from treatments reported in eCRF section *'Concomitant Medications (inclusive of intravitreal injections, systemic Steroids, and IOP medications)'* (CM/F18 form) in the category 'Other'. All ophthalmic treatments other than anti-VEGF, corticosteroids and IOP-lowering medications will be classified as 'Other ophthalmic medications'.

At least one other ophthalmic concomitant medication in the study eye (Yes, No)

This variable will be derived in the same way as the variable *'At least one concomitant anti-VEGF treatment in the study eye (Yes vs. No)'* (See Section 21.3.1).

21.3.3 Variables Related to Lens Status

At least one change in lens status in the study eye during the follow-up period

Using information from eCRF section *'Biomicroscopy – Lens – Study eye'* (BIL/F8 form), the variable will be derived to:

- Yes, if the variable *'1.0 - Have there been any changes to lens status in the study eye to report at this visit?'* is equal to 'Yes' in at least one follow-up visit
- No, if the variable *'1.0 - Have there been any changes to lens status in the study eye to report at this visit?'* is equal to 'No' at all follow-up visits available for the patient
- Missing, if the variable *'1.0 - Have there been any changes to lens status in the study eye to report at this visit?'* is equal to 'Not in Chart' in at least one follow-up visit and is never equal to 'Yes' at the other follow-up visits.

Type of change in lens status in the study eye during the follow-up period

The variable will be defined for all patients with at least one change in lens status from phakic to pseudophakic in the study eye during the follow-up period and will be derived using information collected at baseline and during the follow-up period. For these patients, their baseline measures of lens opacity (nuclear opacity, cortical opacity, and posterior subcapsular opacity) and corresponding grade will be recorded.

21.3.4 Variables Related to Times and Durations

Convention

Time calculated in days will be converted in months using the convention:

1 month = 365.25÷12 days = 30.4375 days

Study duration

The study duration will be derived in months as:

(Date of the last follow-up visit – Date of the first Ozurdex injection in the study eye+1) ÷ (365.25÷12). The result will be rounded to 0.1.

Age at baseline

Age of patient at baseline will be derived in years as:

Year of the first Ozurdex injection in the study eye – Year of birth.

Time to baseline

For a given event E, the time from the event E to baseline will be derived in months as:

(Date of the first Ozurdex injection in the study eye – Date of Event E)÷(365.25÷12). The result will be rounded to 0.1.

This derivation rule will be applied for the following times calculated in months: time from DME diagnosis to baseline, time from onset of DME symptoms to baseline, time from onset of glaucoma to baseline, time from onset of ocular hypertension to baseline, time from the last retinal laser treatment to baseline, time from the last retinal surgery to baseline, time from the last anti-VEGF/Corticosteroid treatment to baseline.

The time from diabetes diagnosis to baseline will be derived in years as:

(Date of the first Ozurdex injection in the study eye – Date of diabetes diagnosis)÷365.25. The result will be rounded to 0.1.

Duration of AESI

The duration will be derived in days as: End date of AESI – Onset date of AESI +1.

Time from the last Ozurdex injection (before or the day of AESI) to AESI

The time will be derived in days as:

Onset date of AESI – Date of the last Ozurdex injection. The last Ozurdex injection will be identified as the last injection among those performed on or before the onset date of the AESI.

21.3.5 Variables Related to BCVA and CRT

BCVA conversion

The method of assessment for BCVA can be reported in the EDC as ETDRS, Snellen (Feet), Snellen (Meters), or Snellen (Decimal). For analysis, all values will be converted into approximate ETDRS letters.

Snellen converted to approximate ETDRS letters = 85 + [50 * log(Snellen fraction)]

BCVA and CRT: Last assessment prior to each Ozurdex injection

For the first Ozurdex injection in the study eye, the last assessment prior to Ozurdex injection (= baseline assessment) is specifically requested in the eCRF. Therefore, the last assessment is directly available.

For subsequent Ozurdex injections in the study eye, the last assessment prior to the j^{th} injection ($j \geq 2$) will be identified considering all assessments available between the day after the $(j-1)^{th}$ injection to the day of the j^{th} injection included (i.e. date of $(j-1)^{th}$ injection < Date of assessment ≤ Date of j^{th} injection). The underlying assumption is that assessments performed at a visit at which an Ozurdex injection is performed are considered as performed before the injection.

BCVA and CRT: Change from baseline to 7-12 weeks following injection j

For each injection j ($j \geq 2$), the change will be calculated as:

Value at 7-12 weeks following injection j – Last value prior to the first (baseline) Ozurdex injection in the study eye. See Section 21.2 for the definition of the '7-12 weeks' time window and for the rule in case of multiple assessments within the time window.

BCVA and CRT: Change from the assessment prior to injection j to 7-12 weeks following injection j

For each injection j ($j \geq 1$), the change will be calculated as:

Value at 7-12 weeks following injection j – Last value prior to Ozurdex injection j. See Section 21.2 for the definition of the '7-12 weeks' time window and for the rule in case of multiple assessments within the time window.

21.3.6 Other Variables Derived From Data Entered in eCRF

Eye with history of steroid response

The variable will be defined from the side of the study eye (OS/OD, eCRF section *'Demographics and DME history'* (DM/F2 form)) and from the variable *'1.3.1. – Specify eye(s)'* (eCRF section *'Ophthalmic history (prior to first Ozurdex injection in Study eye)'* (OH/F4 form)). The variable will be derived to:

- Study eye, if the variable *'1.3.1. – Specify eye(s)'* is equal to the side of the study eye
- Contralateral eye, if the variable *'1.3.1. – Specify eye(s)'* is equal to the side of the contralateral eye
- Both eyes, if the variable *'1.3.1. – Specify eye(s)'* is equal to 'OU (Both)'

Eye with glaucoma, Eye with ocular hypertension

These two variables will be derived in the same way that the variable 'Eye with history of steroid response' (See above).

At least one adverse finding in study eye at biomicroscopy (Yes, No)

Using information from eCRF section *'Biomicroscopy in study eye'* (BIO/F9 form) the variable will be derived to:

- Yes, if the variable *'1.1.2. - Any adverse finding?'* is equal to 'Yes' at baseline or at least once at a follow-up visit
- No, if the variable '1.1.2. - Any adverse finding?' is equal to 'No' at baseline or at all follow-up visits of the patient
- Missing, if the variable *'1.1.2. - Any adverse finding?'* is missing at baseline or at least once at a follow-up visit and is not equal to 'Yes' at the other follow-up visits.

Biomicroscopy in the study eye: adverse finding categorized as 'Present' vs. 'Absent'

For hyperemia, edema (in conjunctiva and cornea), subconjunctival hemorrhage, superficial punctate keratopathy, adverse finding will be considered:

- Absent, if the result is 'Normal'
- Present, if the result is 'Trace +0.5', 'Mild +1', 'Moderate +2' or 'Severe +3'

For cells, adverse finding will be considered:

- Absent, if the result is 'Normal'
- Present, if the result is '+0.5', '+1', '+2', '+3' or '+4'

For flare, adverse finding will be considered:

- Absent, if the result is 'Normal'
- Present, if the result is 'Faint +1', 'Moderate +2', 'Marked +3' or 'Intense +4'

For rubeosis iridis, adverse finding will be considered:

- Absent, if the result is 'Normal'
- Present, if the result is '+0.5', '+1', '+2' or '+3'

At least one adverse finding in study eye at ophthalmoscopic examination (Yes, No)

The variable will be derived in the same way that the variable 'At least one adverse finding in study eye at biomicroscopy during the follow-up period' (See definition above) using information from eCRF section *'Ophthalmoscopic examination in the study eye'* (OE/F10 form).

Ophthalmoscopic examination in the study eye: adverse finding categorized as 'Present' vs. 'Absent'

For cells, haze and hemorrhage in vitreous, adverse finding will be considered:

- Absent, if the result is 'Normal'
- Present, if the result is '+0.5', '+1', '+2', '+3' or '+4'

21.3.7 Variables Derived From Data of the Screening Log

Time from the first Ozurdex implant injection to the most recent follow-up visit prior to 01 September 2018

The variable will be calculated in days as:

Date of the most recent follow-up visit prior to 01 September 2018 – Date of the first Ozurdex injection. As dates are collected in format MM/YYYY, '01' will be considered for the day in the calculation.

21.4 IMPUTATION OF MISSING DATA

Partial date fields with missing day will be imputed as the first of the month. Partial date fields with missing day and month will be imputed as 01JUL.

21.5 OUTLIERS

No adjustment for outliers will be done. Any outliers will be reviewed before the database lock during the data review process and decision documented in the appropriate documentation.

22.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The changes to the analyses specified in the original protocol, dated 24 July 2018, are specified below:

In protocol Section 14.2.2.3.2 it is specified that reason of initial injection and for reinjection will be described. Reason for initial injection is not collected in the eCRF and therefore only reason for reinjection will be described.

No analyses will be performed on the contralateral eye with the exception of AESIs (Section 15.2.4) and select measures of ophthalmic history and current ophthalmic conditions (Section 10.2).

23.0 REFERENCES

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DOCUMENT HISTORY PAGE

Effect Date	Revision Number	Primary Author	Description of Change
24 JUL 2019	V1.0	[redacted]	New