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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)

**Protocol Date:** 24-Jul-2018

# Observational Study Protocol

<b>Study No</b>	CMO-MA-EYE-0564
<b>Product</b>	Dexamethasone intravitreal implant, 0.7 mg (Ozurdex™)
<b>Study Title</b>	Drug Utilization Study in Patients Receiving Ozurdex™ (Dexamethasone Intravitreal Implant) 0.7 mg Injections for Visual Impairment due to Diabetic Macular Edema (DME)
<b>Clinical Phase</b>	Post-marketing study
<b>Study Sponsor</b>	Allergan Pharmaceuticals International Ltd
<b>Date of Protocol</b>	24 JULY 2018
<b>Amendment</b>	Not applicable
<b>Version History</b>	Protocol V1.0 24 JULY 2018

<b>Marketing authorization holder(s)</b>	Allergan Pharmaceuticals Ireland Castlebar Road, Co. Mayo, Westport Ireland
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<b>Responsible Parties</b>	
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[REDACTED]	[REDACTED]
A list of study sites, including principal investigators and co-investigators will be available as a stand-alone document after the beginning of the study.	

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## Approval

### Ozurdex in DME Real-life setting

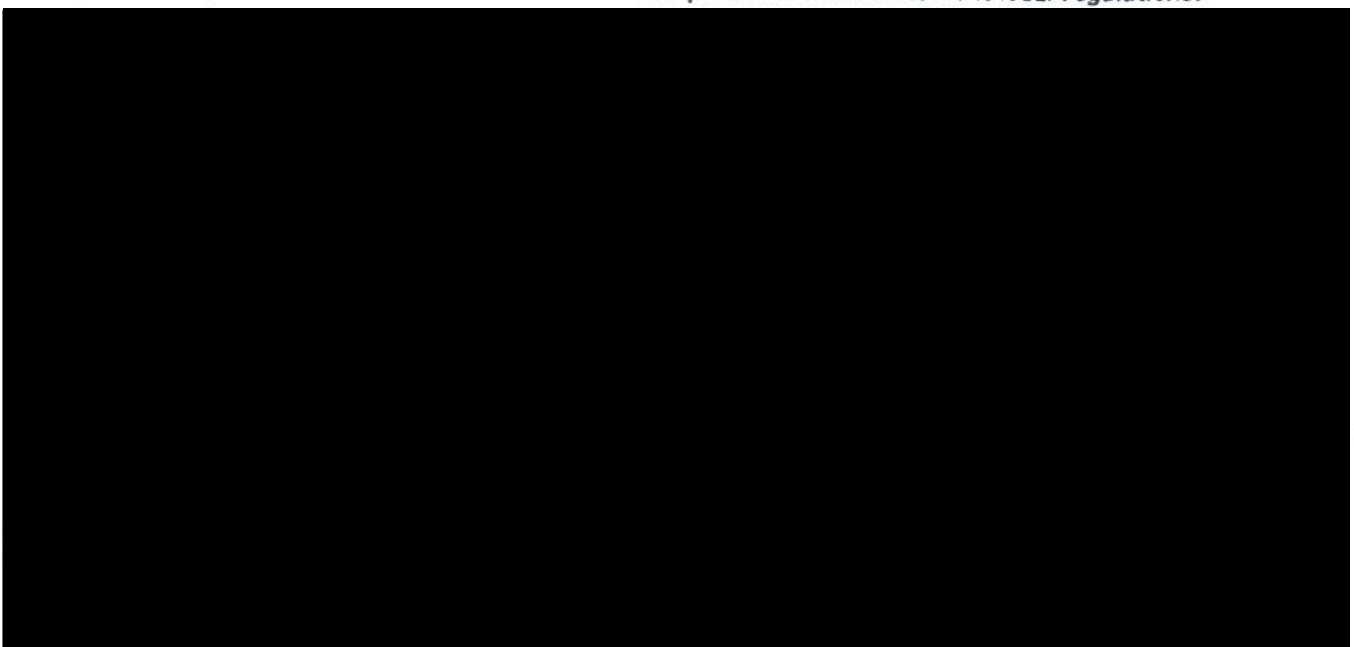
Drug Utilization Study in Patients Receiving Ozurdex™ (Dexamethasone Intravitreal Implant) 0.7 mg Injections for Visual Impairment due to Diabetic Macular Edema (DME)

Protocol N° CMO-MA-EYE-0564

Version 1.0

Dated 24 JULY 2018

The signatures of the advisor-reviewers and representatives of the sponsor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted in compliance with Good Pharmacoepidemiology Practice (GPP) guidelines, the ethical principles arising from the Declaration of Helsinki revised in 2013, the Good Pharmacovigilance practices (GVP), and European and National laws in terms of data protection and all current local regulations.



## Table of contents

<b>Approval.....</b>	<b>2</b>
<b>Table of contents.....</b>	<b>3</b>
<b>List of Tables.....</b>	<b>6</b>
<b>1 SYNOPSIS.....</b>	<b>7</b>
<b>2 LIST OF ABBREVIATIONS .....</b>	<b>12</b>
<b>3 Study Milestones and Timelines.....</b>	<b>14</b>
<b>4 Amendments and Updates .....</b>	<b>15</b>
<b>5 INTRODUCTION .....</b>	<b>15</b>
<b>5.1 Background .....</b>	<b>15</b>
<b>5.2 Study Rationale .....</b>	<b>17</b>
<b>6 OBJECTIVES AND OUTCOME VARIABLES.....</b>	<b>18</b>
<b>6.1 Objectives .....</b>	<b>18</b>
6.1.1 Primary objective.....	18
6.1.2 Secondary objective.....	18
<b>6.2 Outcome Variables .....</b>	<b>18</b>
<b>7 STUDY CONDUCT .....</b>	<b>19</b>
<b>7.1 Overall Design of the Study .....</b>	<b>19</b>
<b>7.2 Patient Discontinuation, Site Termination or Study Termination .....</b>	<b>19</b>
7.2.1 Withdrawal of Individual Patients Prior to Study Completion.....	19
7.2.2 Study or Study Site Termination .....	19
<b>7.3 Bias and Limitations of the Study .....</b>	<b>19</b>
7.3.1 Selection Bias .....	19
7.3.1.1 Sites .....	19
7.3.1.2 Patients .....	20
7.3.2 Information Bias .....	20
7.3.3 Confounding Bias.....	20
<b>8 STUDY POPULATION.....</b>	<b>21</b>
<b>8.1 Sites .....</b>	<b>21</b>
<b>8.2 Patients.....</b>	<b>21</b>
8.2.1 Inclusion Criteria .....	21
8.2.2 Exclusion Criteria.....	21

██████████	██████████	
8.2.4	Minimum Required Dataset .....	22
<b>9</b>	<b>STUDY PROCEDURES .....</b>	<b>23</b>
<b>9.1</b>	<b>Site Selection, Enrollment and Training .....</b>	<b>23</b>
9.1.1	Sampling .....	23
9.1.2	Site Initiation .....	23
9.1.3	Site Monitoring .....	23
<b>9.2</b>	<b>Patient Identification and Selection Procedures .....</b>	<b>24</b>
<b>10</b>	<b>STUDY ASSESSMENTS .....</b>	<b>25</b>
<b>10.1</b>	<b>Data Collected in the Screening Log .....</b>	<b>26</b>
<b>10.2</b>	<b>Demographics .....</b>	<b>26</b>
<b>10.3</b>	<b>Medical and Ophthalmic History .....</b>	<b>26</b>
<b>10.4</b>	<b>Prior and Concomitant Treatments .....</b>	<b>26</b>
10.4.1	Prior and Concomitant Cataract and Glaucoma Procedures .....	26
10.4.2	Prior and Concomitant Laser Therapy .....	26
10.4.3	Prior and Concomitant Other Intravitreal Injections .....	27
10.4.4	Concomitant Medications .....	27
<b>10.5</b>	<b>Clinical Examinations .....</b>	<b>27</b>
<b>10.6</b>	<b>Contralateral Eye .....</b>	<b>27</b>
<b>10.7</b>	<b>Ozurdex Implants .....</b>	<b>27</b>
<b>10.8</b>	<b>Effectiveness Assessments .....</b>	<b>27</b>
10.8.1	Best Corrected Visual Acuity .....	27
10.8.2	Central Retinal Thickness .....	27
<b>10.9</b>	<b>Safety Assessments .....</b>	<b>28</b>
10.9.1	Definitions .....	28
10.9.1.1	<i>Adverse Events .....</i>	28
10.9.1.2	<i>Adverse Reactions .....</i>	28
10.9.1.3	<i>Serious Adverse Drug Reactions .....</i>	28
10.9.1.4	<i>Adverse Events of Special Interest .....</i>	29
10.9.2	Collection and reporting of Safety Events by Investigators .....	29
10.9.3	Case Processing and Submission to Competent Authorities .....	30
<b>11</b>	<b>DATA SOURCES .....</b>	<b>30</b>
<b>12</b>	<b>DATA MANAGEMENT .....</b>	<b>31</b>

<b>13 QUALITY CONTROL .....</b>	<b>31</b>
<b>14 STATISTICAL METHODS.....</b>	<b>32</b>
<b>14.1 Sample Size.....</b>	<b>32</b>
<b>14.2 Study Populations and Analyses.....</b>	<b>33</b>
14.2.1 Study Populations and Analysis Methods .....	33
14.2.2 Planned Analyses.....	34
14.2.2.1 <i>Disposition and Patients' Characteristics</i> .....	34
14.2.2.2 <i>Primary Objective</i> .....	34
14.2.2.3 <i>Secondary Objectives</i> .....	34
14.2.2.3.1 Relationship between Reinjection Intervals and Effectiveness ...	34
14.2.2.3.2 Reason for Ozurdex Implant Initial Injection and for Reinjection	35
14.2.2.3.3 Drug Effectiveness in Patients Naïve of any Anti-VEGF Treatment	35
.....	35
14.2.2.3.4 Adverse Events of Special Interest.....	35
<b>15 ETHICAL CONDUCT OF THE STUDY.....</b>	<b>36</b>
<b>15.1 Ethics Statement .....</b>	<b>36</b>
<b>15.2 Informed Consent .....</b>	<b>36</b>
<b>15.3 Institutional Review Board / Independent Ethics Committee Approval.....</b>	<b>36</b>
<b>15.4 Data Protection .....</b>	<b>36</b>
<b>15.5 Adherence to the Protocol .....</b>	<b>36</b>
<b>15.6 Protocol Amendment.....</b>	<b>37</b>
<b>15.7 Retention of Patient Records .....</b>	<b>37</b>
<b>15.8 Confidentiality .....</b>	<b>37</b>
<b>16 Plans for disseminating and communicating study report .....</b>	<b>37</b>
<b>17 REFERENCES .....</b>	<b>38</b>
<b>APPENDICES .....</b>	<b>40</b>

## List of Tables

Table 1	Study Milestones and Timelines .....	14
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
Table 4	Precision 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 .....	32
Table 5	Precision 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.....	33

## 1 SYNOPSIS

<b>Title</b>	Drug Utilization Study in Patients Receiving Ozurdex™ (Dexamethasone Intravitreal Implant) 0.7 mg Injections for Visual Impairment due to Diabetic Macular Edema (DME) [REDACTED] [REDACTED]
<b>Protocol number</b>	CMO-MA-EYE-0564
<b>Clinical Trials.gov Registration Number</b>	Not yet registered
<b>Planned study dates</b>	Data abstraction is planned to be conducted between third and fourth quarters of 2018.
<b>Objectives</b>	<p><b>Primary objective</b> 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.</p> <p><b>Secondary objectives</b> The secondary objectives of this study are:</p> <ul style="list-style-type: none"> <li>• To assess relationship between reinjection intervals and effectiveness</li> <li>• To describe the reasons for reinjection</li> <li>• To assess drug effectiveness in patients who are naïve of any anti-vascular endothelial growth factor (VEGF) treatment</li> <li>• To present those adverse events of special interest (AESIs) that may be potentially related to Ozurdex reinjection</li> </ul>
<b>Study Design</b>	This 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. The design is based on secondary use of data already collected in medical records for routine clinical care purpose.
<b>Rationale</b>	Drug utilization in real world may not always reflect what has been described in clinical trials. Thus, there is a need for data derived from more heterogeneous patient populations in real-world healthcare settings, such as in observational cohorts, in order to help physicians gain a better understanding of the use of Ozurdex. This retrospective study was designed to assess the reinjection interval of Ozurdex in routine clinical practice in Germany and Switzerland and its relationship with effectiveness and safety of the drug. Study outcomes will enhance knowledge of this treatment option.

<b>Duration of study</b>	For each patient, data abstraction will cover at least one year of follow-up from date of first Ozurdex implant injection up to 1 September 2018. Overall data will be abstracted from 1 January 2015 until 1 September 2018.
<b>Patient Population and Key Selection Criteria</b>	Male and female patients, aged $\geq 18$ years, who received at least 2 Ozurdex implant in the same eye to treat visual impairment due to DME. Among these patients, sites will also be requested to do their best to select a subgroup of up to 50 patients that are naïve to anti-VEGF treatment prior to first Ozurdex implant injection. Patients may contribute at most one eye into the study. If both eyes meet the inclusion criteria, the eye that received the most Ozurdex injections will be chosen as the study eye.
<b>Sample Size</b>	The study aims to select 150 patients. As study primary objective is to assess reinjection interval in real-world, sample size calculation were performed to evaluate the precision around the mean of the reinjection interval.  Considering standard deviations ranging from 1.5 to 3, the selection of 150 patients will enable the description of a mean reinjection interval with satisfactory precisions (half of the 95% confidence interval) ranging from 0.2 to 0.5 months, i.e. from 6 to 15 days (worst case).
<b>Outcome Variables and Assessments</b>	<p><b>Ozurdex Real-word Utilization</b></p> <ul style="list-style-type: none"> <li>Number of Ozurdex implant injections per year</li> <li>Time between Ozurdex implants injections</li> </ul> <p><b>Effectiveness:</b></p> <ul style="list-style-type: none"> <li>Best-corrected visual acuity (BCVA) change from time of injection to 7–12 weeks following each Ozurdex implant injection</li> <li>BCVA change from time of first Ozurdex implant injection to 7–12 weeks following each Ozurdex implant injection</li> <li>Central retinal thickness (CRT) by optical coherence tomography (OCT) change from time of injection to 7–12 weeks following each Ozurdex implant injection</li> <li>CRT by OCT change from time of first Ozurdex implant injection to 7–12 weeks following each Ozurdex implant injection</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>Number and percentage of patients who experienced AESIs</li> <li>[REDACTED]</li> <li>[REDACTED]</li> </ul>

<b>Study Procedures</b>	<p>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 at least one Ozurdex implant injection to help them identify eligible patients.</p> <p>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.</p>
<b>Data Collection Procedures</b>	<p>The following data concerning patient treatment and clinical condition will be collected at the indicated time points.</p> <p><b>Screening Log</b></p> <ul style="list-style-type: none"> <li>• Ozurdex injected to treat visual impairment due to DME</li> <li>• Number of Ozurdex implant injection in each eye</li> <li>• Patient's age at first Ozurdex implant injection</li> <li>• Date (MM YYYY) of first Ozurdex implant injection</li> <li>• Date (MM YYYY) of last follow-up visit</li> <li>• Anti-VEGF injections before first Ozurdex implant injection</li> <li>• Patient received Ozurdex implants as part or during a clinical study</li> <li>• Reason why the patient has not been selected for the study, if applicable</li> </ul> <p><b>Case Report Form</b></p> <p>Relevant data will be collected at baseline, defined as the period prior to first Ozurdex implant injection (index event), and during the study period, defined as the period between the first Ozurdex implant injection and 1 September 2018.</p> <ul style="list-style-type: none"> <li>• Demographics at baseline (age and gender)</li> <li>• Medical and Ophthalmic history (chronic medical conditions and medical conditions ongoing at time of first Ozurdex implant injections, glaucoma, cataract, and lens status)</li> <li>• Prior and concomitant treatments in the study eye (prior and concomitant cataract and glaucoma procedures, prior and concomitant laser therapy, prior and concomitant intravitreal injections other than Ozurdex [including but not limited to anti-VEGF injections], concomitant medications)</li> <li>• Clinical examinations in the study eye (intraocular pressure measurement, biomicroscopic and ophthalmomicroscopic exams performed)</li> <li>• Contralateral eye information (DME status, treatments for DME received prior and during the study period)</li> <li>• BCVA in both eyes at baseline and during the study period</li> <li>• CRT measured in the study eye at baseline and during the study period</li> <li>• Ozurdex implant injections in the study eye during the study period (date of injections and, if available, reason for initial injection and for reinjections)</li> <li>• AESIs: glaucoma, intraocular hypertension, hypotony, cataract or lens</li> </ul>

	<p>opacities, ocular bleeding or hemorrhage, retinal detachment, tear or hole, vitreous detachment, infection vs. non-infection related ocular inflammation, significant vitreous loss, mechanical failure of device and implant misplacement, and implant dislocation.</p> <p>Note: Only high level information on AESIs has been described above. For additional information, please refer to Section 10.9.1.4 in the main body of the protocol.</p>
<b>Statistical Methods</b>	<p><b>Analysis Populations</b></p> <p>Data will be presented for all patients who were selected and met the selection criteria. Data will be presented in the subgroup of patients that are naïve for anti-VEGF treatment; and if the sample size allows it, analyses will also be conducted in a subgroup of patients who received 6 or less anti-VEGF treatments prior to the first Ozurdex implant injection. Additional groups also may be examined, as deemed appropriate.</p> <p><b>Disposition and Patient's Characteristics</b></p> <p>Disposition of patients in the Analysis Population and number of study and contralateral eyes for which data are available will be described.</p> <p><b>Primary Objective</b></p> <p>Number of patients with at least one reinjection and number of reinjections per patient during the year following the first Ozurdex implant injection will be summarized descriptively for all patients from the Analysis population. For patients with more than one year of follow-up, number of patients with at least one reinjection and number of reinjections per patient during the follow-up year considered will be described for each year of follow-up (e.g. 2nd year of follow-up, 3rd year of follow-up...). The number and percentage of patients receiving each injection (first, second, etc.) will be presented for each year of follow-up.</p> <p>Time between Ozurdex implant injections will be summarized overall and for each reinjection, i.e. first reinjection, second reinjection...</p> <p><b>Secondary Objectives</b></p> <p><i>Relationship between Reinjection Intervals and Effectiveness</i></p> <p>Analysis will be performed considering each Ozurdex reinjection separately (second injection or first reinjection, third injection or second reinjection...).</p> <p>Change in BCVA from time of reinjection to 7-12 weeks following reinjection and change in BCVA from time of first injection to 7-12 weeks following reinjection will be summarized for each reinjection. The same analyses will be performed for the change in CRT.</p> <p>A first approach to assess the relationship between reinjections intervals and effectiveness will be to consider time interval between two injections (previous injection - reinjection) as a continuous parameter. The potential relationship between time interval and effectiveness will be assessed graphically using a scatter plot. Time interval between two injections (in months) will be plotted on the horizontal axis and either BCVA change or CRT change from time of reinjection to 7-12 weeks following reinjection will be plotted on the vertical axis. The corresponding correlation coefficients will be calculated. The same scatter plot will be done for the change in BCVA and CRT from time of first implant injection to 7-12 weeks following each Ozurdex</p>

	<p>implant injection.</p> <p>A second approach will be to consider time interval between two injections as a categorical variable; either 2 categories will be considered according to median time interval or other categories will be considered based on observed distribution. BCVA change and CRT change from reinjection to 7-12 weeks following reinjection and BCVA and CRT change from time of first implant injection to 7-12 weeks following each Ozurdex implant injection will be described by these categories.</p> <p><i>Reasons for Ozurdex Implant Initial Injection and for Re[in]jection</i></p> <p>Reason for initial injection and for reinjection of Ozurdex implants will be summarized descriptively.</p> <p><i>Drug Effectiveness in Patients Naïve of any Anti-VEGF Treatment</i></p> <p>Change in BCVA from time of reinjection to 7-12 weeks following reinjection and change in BCVA from time of first injection to 7-12 weeks following reinjection will be summarized for each reinjection considering the subgroup of patients who are treatment naïve of any anti-VEGF treatment. The same will be performed for the change in CRT.</p> <p><i>Adverse Events of Special Interest</i></p> <p>Adverse events of special interest (AESIs) potentially related to Ozurdex reinjection will be summarized descriptively. Number and percentage of patients who experienced AESIs [REDACTED] will be described overall [REDACTED]. [REDACTED]</p>
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The study shall be conducted in compliance with International Society for Pharmacoeconomics and Outcomes Research Good Pharmacoeconomics Practice (ISPE GPP) guidelines, the ethical principles arising from the Declaration of Helsinki revised in 2013, the European Union Good Pharmacovigilance practices (GVP), European and National laws in terms of data protection and all current local regulations. Relevant scientific guidelines such as ENCePP Guide on Methodological Standards in Pharmacoeconomics will be considered.

## 2 LIST OF ABBREVIATIONS

**Abbreviation**

<b>Abbreviation</b>	<b>Definition</b>
ADR	Adverse drug reaction
AE	Adverse event
AEC	Additional exclusion criteria
AESI	Adverse event(s) of special interest
BCVA	Best corrected visual acuity
CI	Confidence interval
CRA	Clinical research associate(s)
CRO	Contract research organization
CRT	Central retinal thickness
DME	Diabetic macular edema
EC	Exclusion criteria
e-CRF	Electronic case report form
EDC	Electronic data capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETDRS	Early treatment diabetic retinopathy study
GPP	Good Pharmacoepidemiology Practice
GVP	Good pharmacovigilance practices
IC	Inclusion criteria
ICH	International conference on harmonization
ICSR	Individual case safety report
IEC	Independent ethics committee
IOP	Intraocular pressure
ISPE	International society for pharmacoepidemiology
MAH	Marketing authorization holder
MAR	Minimum angle of resolution
MedDRA	Medical dictionary for regulatory activities
OCT	Optical coherence tomography
OU	Oculus uterque
SADR	Serious adverse drug reaction

SAP	Statistical analysis plan
SD	Standard deviation
SE	Study eye
SUSAR	Suspected unexpected serious adverse reactions
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

### 3 STUDY MILESTONES AND TIMELINES

The planned study milestones and timelines are described in Table 1 below.

**Table 1 Study Milestones and Timelines**

Milestone	Estimated Date
Ethics submission	Third quarter 2018
Start of data collection <sup>[a]</sup>	Third quarter 2018
End of data collection <sup>[b]</sup>	Fourth quarter 2018
Final Report of study results	Second quarter 2019

[a] Date of start of data collection will be considered as the first patient entered in the eCRF

[b] Date of end of data collection will be considered as date of database lock.

## 4 AMENDMENTS AND UPDATES

This section is not applicable (original protocol).

## 5 INTRODUCTION

### 5.1 Background

Ozurdex® is a biodegradable solid polymer drug delivery system containing 0.7 mg of dexamethasone. A single-use applicator with a 22-gauge needle that leaves a sutureless self-sealing wound is used to place the dexamethasone implant into the vitreous cavity. The sustained-release formulation was designed to release dexamethasone from the implant for up to 6 months. Ozurdex was granted a marketing authorization in the European Union in 2010 for the treatment of adult patients with macular edema following vein occlusion. In 2011, Ozurdex was furthermore approved for treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. More recently, in 2014, Ozurdex was approved for treatment of adult patients with visual impairment due to diabetic macular edema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy<sup>1</sup>.

DME is a common manifestation of diabetic retinopathy; diabetic retinopathy being microvascular abnormalities seen in the fundus of persons with diabetes. In most studies, DME is defined by hard exudates in the presence of microaneurysms and blot hemorrhages, resulting in increased central retinal thickness (CRT) within one disc diameter of the foveal center. Clinically significant macular edema is the most severe spectrum of DME, and was defined by the presence of edema within 500 µm of the foveal center, or focal photocoagulation scars present in the macular area. The prevalence of DME in population-based studies among type-1 diabetes patients varied between 4.2% and 7.9%<sup>2</sup>. In patients with type-2 diabetes it was between 1.4% and 12.8%. DME is a leading cause of serious central visual loss impairment in diabetic patients. Due to worldwide rise of diabetes mellitus and of life expectancy of those with diabetes mellitus, burden of illness of microvascular complications, such as DME, is expected to increase over time.

Clinical evaluation of DME may be difficult and subjective. Gold standard for DME diagnostic still remains the fluorescein angiography, but optical coherence tomography (OCT) can be used for screening, classification, monitoring, and treatment evaluation of the DME. It has the ability to provide information on CRT as well as distinct morphological features of the edema.

The chance of spontaneous improvement in the best-corrected visual acuity (BCVA) and decrease in CRT is limited, so the prognosis of DME without appropriate treatment is generally disappointing. Several therapeutic options are available. Focal and grid laser photocoagulation has represented the standard of care for treatment of DME prior to the introduction of intravitreal approach, i.e. anti-vascular endothelial growth factor (anti-VEGF) and corticosteroids. Approved anti-VEGF therapies include ranibizumab (Lucentis®, Novartis) and afibbercept (Eylea®, Bayer HealthCare). Even though not currently approved, bevacizumab (Avastin®, Genetech/Roche) is also used off-label for the treatment of retinal diseases, including DME<sup>3,4</sup>. Anti-VEGF agents restore vision in a substantial proportion of treated patients<sup>5,6</sup>. However, drawbacks have been identified for anti-VEGF patients: patients treated with anti-VEGF may be at increased risk to develop systemic (thromboembolic) adverse events (AEs) compared with sham/laser treatment arms<sup>7</sup>; treatment

with anti-VEGF require monthly injections at the clinic for an extended period of time; and some patients are partial or non-responders to anti-VEGF treatments<sup>8,9</sup>. Corticosteroids therapy, through anti-inflammatory properties, and VEGF inhibition, inhibit many of the inflammatory processes known to be involved in the progression of DME. Commercially available corticosteroids compounds for intravitreal use include fluocinolone (Iluvien<sup>®</sup>, Alimera Sciences) and Ozurdex<sup>®</sup>. Even though not approved for this indication, triamcinolone acetonide is also used off-label for the treatment of DME. Long-acting corticosteroid implants such as Iluvien and Ozurdex have the benefit of reducing the number and frequency of injections<sup>10,11</sup>. In the European Society of Retina Specialists (EURETINA) guidelines for the management of DME, the importance of corticosteroids in the armamentarium of drugs for treating DME patients is recognized; however corticosteroids are recommended to be administered in non-responders who have already been treated with anti-VEGF. First line therapy with Ozurdex should be considered in patients with history of major cardiovascular events and in patients that are not willing to come for monthly injections in the first 6 months of therapy<sup>5</sup>.

Ozurdex efficacy in patients with visual impairment due to DME was assessed in 2 randomized, multi-center, masked, sham-controlled, phase III trials, the MEADs trials, over a 3-year period<sup>12</sup>. At study end, 22.2% of patients who received Ozurdex (N=351) had a ≥15-letter improvement compared to 12.0% in the sham group (N=350) ( $p<0.001$ ). Mean BCVA average change over the 3-year period was higher in patients treated with Ozurdex (3.5 letters) than in the sham group (2.0 letters) ( $p=0.023$ ). Mean average reduction in CRT from baseline was greater with Ozurdex 0.7 mg (-111.6  $\mu$ m) than with sham (-41.9  $\mu$ m). In a prospective, multi-center, open-label, 1-year follow-up study, the CHAMPLAIN trial, 27 treatment-naïve patients with type-2 diabetes and affected by DME were treated with Ozurdex<sup>13</sup>. During the one-year follow-up period, most patients (66%) received a second Ozurdex injection with a mean time between injections of  $6.7\pm2.3$  months. One month after the first injection BCVA significantly improved compared to baseline (-0.02 LogMAR) and CRT significantly decreased (-79  $\mu$ m).

In the MEADs trials, the most commonly reported AEs following treatment with Ozurdex are those frequently observed with ophthalmic steroid treatment or intravitreal injections: cataract formation, elevated intra-ocular pressure (IOP), and conjunctival or vitreal hemorrhage<sup>12</sup>. In these trials, cataract-related AEs were observed in 67.9% of patients with a phakic eye at baseline compared to 20.4% of patients in the sham group. The incidence of cataract-related AEs increased after the first year after Ozurdex injection. Approximately one-third of patients with Ozurdex implant had a clinically significant increase in IOP requiring treatment during the study. Vitreous hemorrhage considered possibly related to treatment was reported in 3.5% of patients with Ozurdex implant compared to 0.0% in the sham group. Less frequently reported but more serious adverse drug reactions include endophthalmitis, necrotizing retinitis, retinal detachment and retinal tear. With the exception of headache and migraine, no systemic adverse drug reactions were identified with the use of Ozurdex. Finally, several adverse drug reactions, such as conjunctival hemorrhage, visual acuity reduced, vitreous detachment, vitreous floaters, vitreous opacities, eye pain, photopsia, conjunctival edema, conjunctival hyperemia, endophthalmitis, retinal detachment, retinal tear, hypotony of the eye, anterior chamber inflammation, anterior chamber cells/flare, abnormal sensation in eye, scleral hyperemia, device dislocation, and complication of device insertion, have been identified in Ozurdex SmPC as related to the intravitreal injection procedure<sup>1</sup>, i.e. the frequency of these AEs is proportional to the number of treatments given.

## 5.2 Study Rationale

Ozurdex efficacy and safety have previously been shown in PLACID, MEAD and CHAMPLAIN clinical trials. While large phase 3 clinical trials are fundamental to supporting the registration of new drugs, these studies were performed in highly selected patients under well controlled conditions. In MEADs clinical trials, patients were eligible for retreatment if it had been at least 6 months since the previous study treatment. Drug utilization in real world may not always reflect what has been described in clinical trials. Thus, there is a need for data derived from more heterogeneous patient populations in real-world healthcare settings, such as in observational cohorts, in order to help physicians gain a better understanding of the use of Ozurdex. This retrospective study was designed to assess the reinjection interval of Ozurdex in routine clinical practice in Germany and Switzerland and its relationship with effectiveness and safety of the drug. Study outcomes will enhance knowledge of this treatment option.

## 6 OBJECTIVES AND OUTCOME VARIABLES

The study objectives were not based on any hypothesis.

### 6.1 Objectives

#### 6.1.1 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.

#### 6.1.2 Secondary objective

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 reinjection

### 6.2 Outcome Variables

Ozurdex Real-word Utilization

- Number of Ozurdex implant injections per year
- Time between Ozurdex implants injections

Effectiveness:

- BCVA change from time of injection to 7-12 weeks following each Ozurdex implant injection
- BCVA change from time of first Ozurdex implant injection to 7-12 weeks following each Ozurdex implant injection
- CRT by OCT change from time of injection to 7-12 weeks following each Ozurdex implant injection
- CRT by OCT change from time of first Ozurdex implant injection to 7-12 weeks following each Ozurdex implant injection

Safety:

- Number and percentage of patients who experienced AESIs



## 7 STUDY CONDUCT

### 7.1 Overall Design of the Study

This 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 at least one Ozurdex implant injection after the 1 January 2015 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.

Study procedures, and evaluations are described in detail in Sections 9 to 11 and data to be collected are summarized in Table 2. Safety events to be collected are described in Section 10.9.

### 7.2 Patient Discontinuation, Site Termination or Study Termination

#### 7.2.1 Withdrawal of Individual Patients Prior to Study Completion

Considering the retrospective study design, no withdrawal of individual patients prior to study termination is expected.

#### 7.2.2 Study or Study Site Termination

The Sponsor reserves the right, at any time, to discontinue selection of additional patients into the study, at any site; or to discontinue the study for administrative reasons.

### 7.3 Bias and Limitations of the Study

#### 7.3.1 Selection Bias

##### 7.3.1.1 Sites

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, a non-response selection bias is possible.

### **7.3.1.2 Patients**

In order to limit 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 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 Sections 9.2 and 10.1). 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 met selection criteria, lack of time, quotas were met, etc.).

### **7.3.2 Information Bias**

Information bias is a distortion in the estimate of association between risk factor and disease that is 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, the study will rely on data that have already been collected for another purpose (e.g. 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 data variables collected during the chart review process may be heterogeneous across sites. This could potentially introduce a systematic bias into the results and would likely result in greater variability in the study result (e.g. OCT method used to measure CRT or method used to measure BCVA).

Information bias can be minimized by the use of electronic data capture technology. In addition to minimize the burden on the investigators and the sites, electronic data capture technology will maximize the quality and relevance of the data using automated online controls (e.g., automated controls on value ranges, units, internal consistency, and missing key data). To complement automated online controls, principal investigators will be requested to review all entered data submitted in the electronic data capture system.

### **7.3.3 Confounding Bias**

Confounding bias may result from selective prescribing of a particular treatment to more severely affected patients. As a result of a higher background risk, reported event rate may be higher and give the appearance of an elevated risk related to the use of the 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 incidence of 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 or use of Ozurdex (e.g. previous occurrence of glaucoma, previous cataract, previous anti-VEGF treatment).

## 8 STUDY POPULATION

### 8.1 Sites

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.

### 8.2 Patients

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 criteria, the eye that received the most Ozurdex injections will be chosen as the study eye.

#### 8.2.1 Inclusion Criteria

A patient must meet **all** of the following criteria to be eligible for participation in the study.

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  $\geq 18$  years at time of first Ozurdex implant injection
3. First Ozurdex implant injection occurred after 1 January 2015
4. Patient was followed-up at the site for at least 12 months after the first Ozurdex implant in the study eye

#### 8.2.2 Exclusion Criteria

A patient who meets the following criteria is not eligible for participation in the study.

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

[REDACTED]

[REDACTED]

[REDACTED]

### **8.2.4 Minimum Required Dataset**

#### **Ozurdex Real-word Utilization (in study eye)**

- Number of Ozurdex implant injections
- Date of Ozurdex implant injections
- BCVA prior to injection time and following each Ozurdex implant
- Receipt of concomitant DME treatment in the study eye

#### **Patient characteristics**

- Age
- Gender
- Date of DME diagnosis in the study eye

#### **Other treatment**

- Prior and concomitant other intravitreal injections (if relevant)

## **9 STUDY PROCEDURES**

### **9.1 Site Selection, Enrollment and Training**

#### **9.1.1 Sampling**

Allergan will identify sites among experienced medical retina centers treating DME patients. Sites will be identified using Allergan field-based knowledge.

The study will be proposed to all the sites identified by Allergan; a recruitment mail containing the study summary, the site qualification questionnaire and a reply coupon will be sent to all these sites. If the return rate is insufficient, non-responders will be contacted by telephone to fill out the site qualification questionnaire.

The Sponsor or designee will qualify sites with sufficient resources (time, personnel, and facilities) to participate in the study. Sites will be required to obtain approval from the appropriate Independent Ethics Committee (IEC), and will be responsible for maintaining all related documents, before enrollment of any patient into the study.

Recruitment will end as soon as approximately 10 sites, 7 in Germany and 3 in Switzerland, are qualified to participate in the study.

#### **9.1.2 Site Initiation**

Sites will receive a study kit once all the necessary administrative procedures have been completed (confidentiality agreement, research contract agreement, curriculum vitae... where applicable).

The study kit contains the study protocol and the e-CRF user manual. On reception of the study kit, an initiation telephone call will be organized by Clinical Research Associates (CRA) to explain the protocol, data collection, and the practical aspects of the study.

In addition, designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, data protection, and the electronic data capture (EDC) system. Retraining will be conducted as needed.

#### **9.1.3 Site Monitoring**

During the chart-extraction period, sites will be contacted by telephone by CRAs to follow the site identification of patients, the e-CRF completion and to answer any questions sites may have concerning data to be collected and the logistics of the study. Frequency of telephone calls will be site dependent and based on identified needs for each site. A close out call will be performed by CRAs at the end of the study. Site monitoring processes will be further detailed in the Site Management and Monitoring Plan.

## 9.2 Patient Identification and Selection Procedures

Medical charts will be screened by the investigative site personnel to identify patients who satisfy all the inclusion and none of the exclusion criteria. Once a site has been initiated, 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<sup>1</sup>. Data collected in the screening log, listed in Section 10.1, will help site personnel identify eligible patients. Screening logs will be anonymized before being entered in the study database.

### *Non-competitive selection of eligible patients*

Upon screening log completion, the sites will proceed through the patients listed in the screening log and will select all consecutive patients who meet the inclusion criteria (Section 8.2.1) and none of the exclusion criteria (Section 8.2.2), starting with patients who received their first Ozurdex injection the closest to 1 January 2015. Patient selection will not be competitive between countries and will stop when the quotas of eligible patients has been reached in each country, i.e. approximately 70 patients in Germany and 30 patients in Switzerland. 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.

### *Competitive selection of patients - patients who are naïve to anti-VEGF treatment*

During the patient selection process, special attention will be given to patients that are naïve to anti-VEGF treatment prior to first Ozurdex implant injection [REDACTED]

[REDACTED], and sites will be asked to do their best to select a predetermined number of patients who do not meet this exclusion criteria. Recruitment of patients that are naïve to anti-VEGF treatment will stop when approximately 50 patients have been selected in Germany and Switzerland.

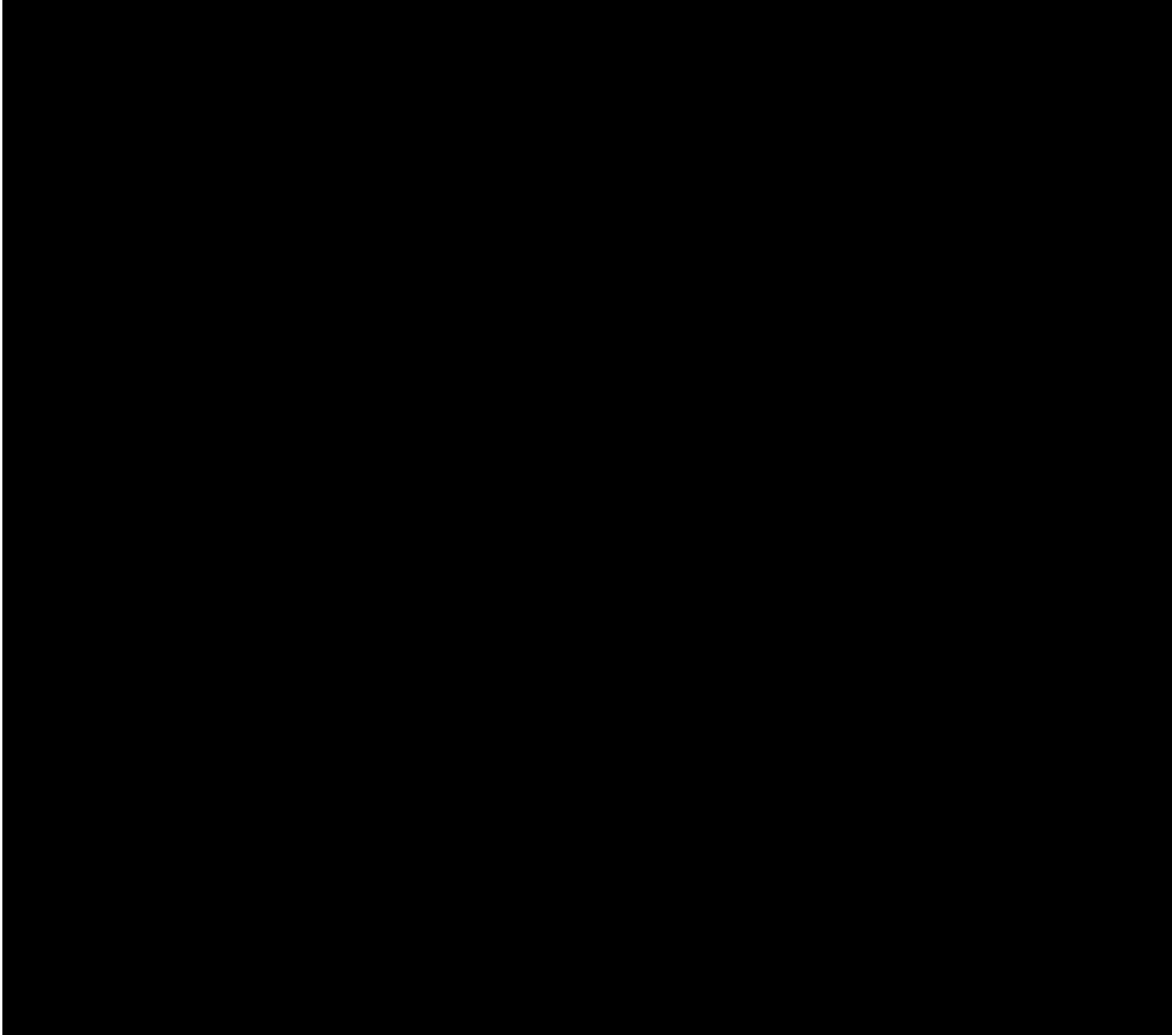
Overall, patient selection will stop when 150 patients have been selected for the study. The number of patients included at each site, in particular the number of patients that are naïve to anti-VEGF treatment, will be chosen based on feasibility surveys and consultations with the Sponsor.

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<sup>1</sup> 1 September 2017 was chosen to get at least 1 year of follow-up data on 1 September 2018 for all selected patients.

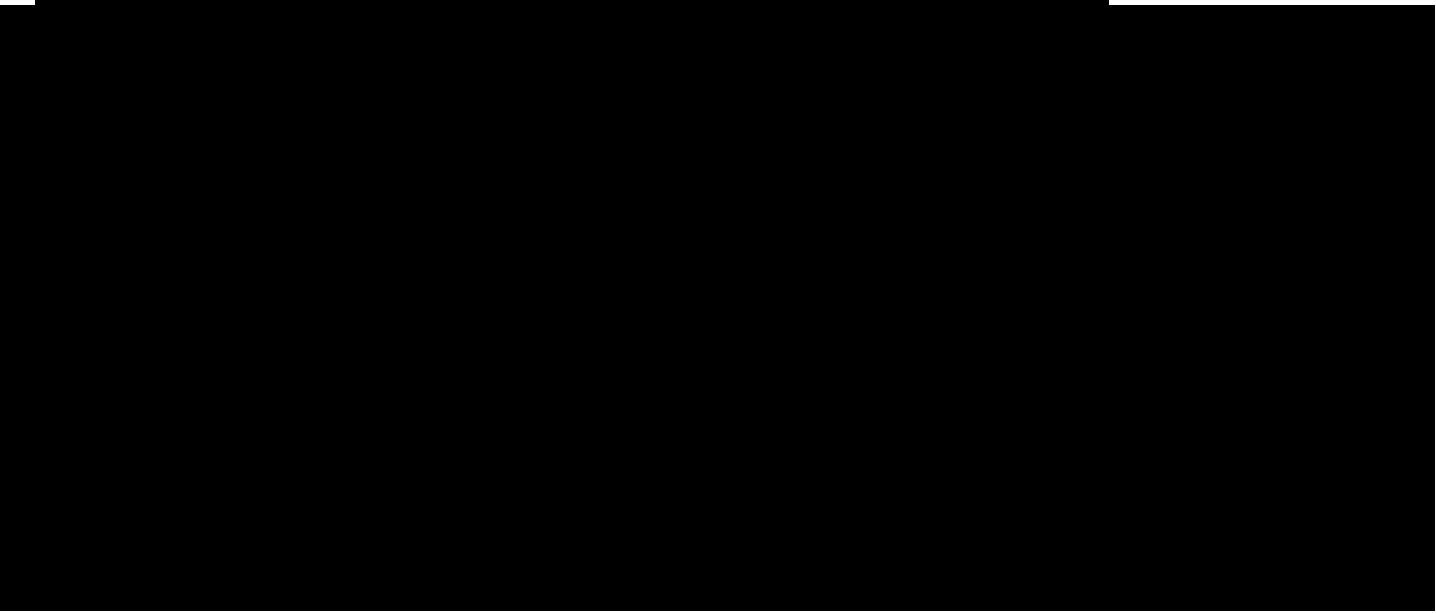
## 10 STUDY ASSESSMENTS

This is a retrospective, observational study and patient data collected from the sites will be abstracted from medical charts. Baseline will be defined as the period prior to first Ozurdex implant injection (index event) and study period will be defined as the period between the first Ozurdex implant injection and 1 September 2018.



## 10.1 Data Collected in the Screening Log

Once a site has been initiated, site personnel will be invited to complete a screening log with all patients who received at least one Ozurdex implant injection. [REDACTED]



## 10.2 Demographics

Patients' age at first Ozurdex implant injection and gender will be recorded in the eCRF.

## 10.3 Medical and Ophthalmic History

Chronic medical conditions and medical conditions ongoing at time of first Ozurdex implant injection will be collected, along with year of onset. History of glaucoma, cataract and lens status (phakic or pseudophakic) will be collected.

DME history, i.e. date of onset of symptoms and date of DME diagnosis in the study eye, will be collected.

## 10.4 Prior and Concomitant Treatments

### 10.4.1 Prior and Concomitant Cataract and Glaucoma Procedures

Cataract and glaucoma procedure performed on the study eye prior to the study period and during the study period will be recorded (e.g., cataract surgery, glaucoma laser, trabeculectomy, glaucoma valve implant, laser peripheral iridotomy, other procedures).

### 10.4.2 Prior and Concomitant Laser Therapy

Focal/grid laser treatments for DME occurred on the study eye prior to the study period and during the study period will be recorded (date of treatment, focal or grid laser photocoagulation).

#### **10.4.3 Prior and Concomitant Other Intravitreal Injections**

Intravitreal injections other than Ozurdex received prior to study period will be recorded for the study eye: name, number of treatments, and last treatment date.

At each visit occurred during the study period, intravitreal injections other than Ozurdex received in the study eye will be recorded.

Special focus will be placed on the following intravitreal injections:

- Anti-VEGF therapies such as Lucentis®, Eylea®, and Avastin®
- Corticosteroid therapies other than Ozurdex such as Iluvien® and triamcinolone

#### **10.4.4 Concomitant Medications**

A pre-defined list of concomitant medications that may have an impact on short term efficacy and safety of the drug received at time of first Ozurdex implant administration and during the study period will be recorded (inclusive of IOP medications, corticoid medications, non-steroid anti-inflammatory drug, immunosuppressive drug, and antithrombotic agents) : medication name, start date, end date, indication (eye condition vs. other medical condition).

### **10.5 Clinical Examinations**

Biomicroscopic and ophthalmomicroscopic exams performed in the study eye (yes/no), and intraocular pressure value measured in the study eye will be collected at baseline and at each visit occurred during the study period.

### **10.6 Contralateral Eye**

DME status in the contralateral eye will be recorded at baseline and at all visits occurred during the study period.

Treatments for DME received prior to study period will be recorded for the contralateral eye. For each visit occurred during the study period, treatments received in the contralateral eye (inclusive of intravitreal treatment) will be recorded.

### **10.7 Ozurdex Implants**

For each Ozurdex implant injection performed in the study eye, date of injection will be recorded. If available, reason for initial injection and reinjections will be collected.

### **10.8 Effectiveness Assessments**

#### **10.8.1 Best Corrected Visual Acuity**

BCVA will be collected at baseline and at all visits during the study period in both study and contralateral eyes. Values will be recorded in the eCRF according to local practice (Snellen, MAR, EDTRS, etc.) along with scale name or method used to assess BCVA.

#### **10.8.2 Central Retinal Thickness**

CRT measured in the study eye will be collected at baseline and at all visits during the study period if it was measured using OCT. Technology and device brand used to measure OCT will also be collected.

## 10.9 Safety Assessments

### 10.9.1 Definitions

#### 10.9.1.1 Adverse Events

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of this medicinal product (see GVP Annex IV, ICH-E2D guideline<sup>14</sup>).

#### 10.9.1.2 Adverse Reactions

An **adverse reaction** is a response to a medicinal product which is noxious and unintended [DIR2001/83/EC Art 1(11)] (see GVP Annex I, Definitions<sup>15</sup>). Synonyms are adverse drug reactions (ADR), suspected adverse (drug) reaction, adverse effect, and undesirable effect. Response in this context means that causal relationship between the medical product and an AE is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline 5<sup>16</sup>). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

For regulatory reporting purposes on post approval safety data, if an AE is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an ADR.

#### 10.9.1.3 Serious Adverse Drug Reactions

An SADR is an ADR that meets any of the following criteria (see GVP Annex IV, ICH-E2A Guideline 5<sup>16</sup>):

- Results in **Death** of patient.
- Is **life-threatening**: this refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization**: An event/reaction that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- Results in **prolongation of existing hospitalization**: An event/reaction that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
- Is a **congenital anomaly/birth defect**: An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- Results in **persistent or significant disability/incapacity**: An event/reaction that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

- Is a **medically important event or reaction**: An important medical event/reaction that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly/birth defect, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Any **suspected transmission via a medicinal product of an infectious agent** is also considered as a SADR

#### **10.9.1.4 Adverse Events of Special Interest**

An AE of special interest (AESI) (serious or non-serious) is an AE specific to the sponsor's product or program. Such an event might warrant further investigation to characterize and understand it.

#### **10.9.2 Collection and reporting of Safety Events by Investigators**

The study will be conducted in accordance with Directive 2001/83/EC, Regulation (EC) No 726/2004, Commission Implementing Regulation (EU) No 520/2012 as amended and detailed in GVP Modules VI<sup>17</sup>.

Considering that study aims to explore the potential impact of recurrent Ozurdex injections, and not confirm the whole safety profile, and considering the current knowledge of the study drug safety profile, this study focuses only on the following AESIs (related or not to Ozurdex):

- **Glaucoma**, defined as damage to the optic nerve with progressive vision loss (open angle glaucoma, normal tension glaucoma, and acute angle closure glaucoma)
- **Intraocular hypertension**, defined as IOP without meeting the criteria for glaucoma
- **Hypotony**, defined as low IOP  $\leq 5$  mmHg
- **Cataract or lens opacities** (nuclear sclerotic, cortical and posterior subcapsular)
- **Ocular bleeding or hemorrhage** (conjunctival, anterior chamber, vitreous, macular, retinal)
- **Retinal detachment, tear or hole**
- **Vitreous detachment**
- **Infection vs. Non-infection related Ocular inflammation** (conjunctivitis, blepharitis, episcleritis, scleritis, keratitis, uveitis, retinitis and endophthalmitis)
- **Significant vitreous loss**
- **Mechanical failure of device and implant misplacement**
- **Implant dislocation**

In addition to AESIs, off-label use should be collected, and reported to Allergan whether or not off-label use was associated with an AE.

Due to the retrospective design of the study, the reporting of safety events to the sponsor is not solicited for this study. However, investigators are reminded about the possibility for them to report

any suspected ADRs directly to the marketing authorization holder of the suspected medicinal product (studied or not) or to the concerned competent authority via the national spontaneous reporting system.

#### **10.9.3 Case Processing and Submission to Competent Authorities**

In accordance with GVP Module VI.C.1.2.1.2<sup>17</sup> (non-interventional post-authorization studies with a design based on secondary use of data) the submission of suspected ADRs in the form of individual case safety reports (ICSRs) is not required. Therefore, Allergan will not submit any ICSRs for solicited ADRs collected for the study. However, all AEs/ADRs collected for the study will be recorded in the study database and summarized in study reports.

The investigators are responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IEC that approved the study.

## **11 DATA SOURCES**

This is a retrospective, observational study, and patient data collected from the sites will be abstracted from medical charts.

## 12 DATA MANAGEMENT

All data collected in the context of this study will be stored and evaluated in accordance with regulatory requirements and applicable guidance for electronic records.

Electronic data collection will be performed using an e-CRF. Investigators or study personnel will enter data into the electronic data capture (EDC) system according to the schedule of assessments (Table 2) and according to instructions from the Sponsor and/or designee. Only authorized personnel will have access to the EDC system. Data will be anonymized and once entered in the system, investigators and study personnel will not be able to identify patients.

Each investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner. Specific processes used to manage the data throughout the study will be documented in the Data Management Plan. Briefly, on-line logic checks will be built into the system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, no queries will be issued as investigators will not be able to connect the patient with his/her identification number. Consequently, to prevent as much as possible remaining inconsistent data, all data entered into the eCRF should be reviewed by the principal investigator. The principal investigator will be responsible for endorsing data within the eCRF. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

Medical history, concomitant disease, and AEs will be coded, using Medical Dictionary for Regulatory Activities (MedDRA, the most recent version). Drugs will be coded with the WHO Drug Dictionary.

A final validation of the database will be performed, and the database will be locked, before the statistical analysis is conducted.

## 13 QUALITY CONTROL

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative site and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, and the EDC system. Retraining will be conducted as needed.

The Sponsor and its representatives will monitor the study over the telephone on a regular basis, according to the Monitoring Plan. At the monitoring visits, the progress of the study and any procedural or data issues will be discussed with the site and/or designee (see Section 9.1.3).

Quality controls performed during statistical analyses will be described in the statistical analysis plan (SAP).

Secure electronic archive will be maintained and will include but will not be limited to: final raw data, analysis datasets, programs and associated documentation. Access to the archive will be controlled and limited to authorized personnel only.

## 14 STATISTICAL METHODS

### 14.1 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 diabetic macular edema in real-world. Matropasqua et al.<sup>13</sup> reported a mean  $\pm$  standard deviation (SD) of  $6.7 \pm 2.3$  months in 27 Italian patients. Querques et al.<sup>18</sup> 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 ( $\pm$ SD) of  $4.8 \pm 1.8$ <sup>2</sup> months between reinjections based on data from 111 French ophthalmologists who completed a survey about their practice.

The precision of the 95% confidence interval (CI) of the mean ( $\omega$ , half of the width of the CI) is determined using the following formula:

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

Table 4 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 4 Precision 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 (month)				
	$\omega$	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. 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],  $\omega = 15$  days).

<sup>2</sup> Standard deviation was not clearly available in the paper and was recalculated from available data.

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<sup>19</sup> reported a difference in visual acuity from baseline to 6 months (mean  $\pm$  SD) of  $11.5 \pm 4.6$  ETDRS letters in 36 treatment naïve patients whereas in 2018 Iglicki et al.<sup>20</sup> reported a gain at 24 months (mean  $\pm$  SD) of  $11.3 \pm 10.0$  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, standard deviation ranging from 4.5 to 10.0 and a sample size of 50 patients (Table 5).

**Table 5 Precision 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	$\omega$	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, 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.

## 14.2 Study Populations and Analyses

A formal SAP that will provide details of all analyses and presentation of study data will be approved prior to data analysis. Statistical analysis will be carried out using SAS software version 9.2 or later.

### 14.2.1 Study Populations and Analysis Methods

- Analysis Population: data will be summarized for all patients who were selected and met the selection criteria.
- Subgroups analysis will be conducted in patients who are naïve for anti-VEGF treatment. If the sample size allows it, analyses will also be conducted in a subgroup of patients who received 6 or less anti-VEGF treatments prior to the first Ozurdex implant injection.
- Additional groups also may be examined, as deemed appropriate such as according to lens status at baseline (phakic vs. pseudophakic) or according to concomitant treatments (concomitant anti-VEGFs vs. Ozurdex only).

Continuous variables will be described by their mean, SD, median, first and third quartiles, extreme values (minimum and maximum) and the number of missing data.

Categorical variables will be described by the total and percentage of each response and the number of missing data.

Two-sided 95% CI of the mean and of percentage may also be calculated when appropriate. Data may also be presented graphically when relevant.

## **14.2.2Planned Analyses**

### **14.2.2.1 Disposition and Patients' Characteristics**

Disposition of patients in the Analysis Population and number of study and contralateral eyes for which data are available will be described.

Clinical examinations, prior and concomitant treatments, and contralateral eye data will be summarized descriptively.

### **14.2.2.2 Primary Objective**

Number of patients with at least one reinjection and number of reinjections per patient during the year following the first Ozurdex implant injection will be summarized descriptively for all patients from the Analysis population. For patients with more than one year of follow-up, number of patients with at least one reinjection and number of reinjections per patient during the follow-up year considered will be described for each year of follow-up (e.g. 2<sup>nd</sup> year of follow-up, 3<sup>rd</sup> year of follow-up...). The number and percentage of patients receiving each injection (first, second, etc.) will be presented for each year of follow-up.

Time between Ozurdex implant injections will be summarized overall and for each reinjection, i.e. first reinjection, second reinjection...

### **14.2.2.3 Secondary Objectives**

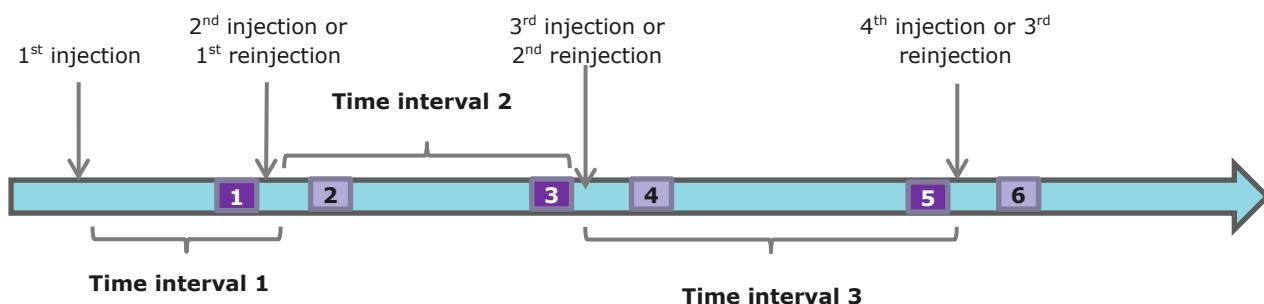
#### **14.2.2.3.1 Relationship between Re[in]jection Intervals and Effectiveness**

Analysis will be performed considering each Ozurdex reinjection separately (second injection or first reinjection, third injection or second reinjection...) (see Figure 1).

Change in BCVA from time of reinjection to 7-12 weeks following reinjection and change in BCVA from time of first injection to 7-12 weeks following reinjection will be summarized for each reinjection. The same analyses will be performed for the change in CRT.

A first approach to assess the relationship between reinjections intervals and effectiveness will be to consider time interval between two injections (previous injection - reinjection) as a continuous parameter. The potential relationship between time interval and effectiveness will be assessed graphically using a scatter plot. Time interval between two injections (in months) will be plotted on the horizontal axis and either BCVA change or CRT change from time of reinjection to 7-12 weeks following reinjection will be plotted on the vertical axis. The corresponding correlation coefficients will be calculated. The same scatter plot will be done for the change in BCVA and CRT from time of first implant injection to 7-12 weeks following each Ozurdex implant injection.

**Figure 1 Example of Reinjections Intervals and Effectiveness Outcomes Disposition in a Hypothetic Patient**



BCVA=Best corrected visual acuity; CRT=Central retinal thickness

- Last BCVA and CRT measured before injection of Ozurdex
- BCVA and CRT measured 7 to 12 weeks following each reinjection

For "Time interval 1", BCVA and CRT change from measurement 1 to measurement 2 will be considered; for "Time interval 2" BCVA and CRT change from measurement 3 to measurement 4 will be considered; and for "Time interval 3", BCVA and CRT change from measurement 5 to measurement 6 will be considered.

A second approach will be to consider time interval between two injections as a categorical variable; either 2 categories will be considered based on median time interval or other categories will be considered based on observed distribution. BCVA change and CRT change from reinjection to 7-12 weeks following reinjection and BCVA and CRT change from time of first implant injection to 7-12 weeks following each Ozurdex implant injection will be described by these categories.

#### 14.2.2.3.2 Reason for Ozurdex Implant Initial Injection and for Reinjection

Reason for initial injection and for reinjection of Ozurdex implants will be summarized descriptively.

#### 14.2.2.3.3 Drug Effectiveness in Patients Naïve of any Anti-VEGF Treatment

Change in BCVA from time of reinjection to 7-12 weeks following reinjection and change in BCVA from time of first injection to 7-12 weeks following reinjection will be summarized for each reinjection considering the subgroup of patients who are treatment naïve of any anti-VEGF treatment. The same will be performed for the change in CRT.

#### 14.2.2.3.4 Adverse Events of Special Interest

Adverse events of special interest (AESIs) potentially related to Ozurdex reinjection will be summarized descriptively. Number and percentage of patients who experienced AESIs

will be described overall [REDACTED]. [REDACTED]

## 15 ETHICAL CONDUCT OF THE STUDY

### 15.1 Ethics Statement

The study shall be conducted in compliance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Pharmacoeconomics and Outcomes Research Practice (GPP) guidelines<sup>21</sup>, the ethical principles arising from the Declaration of Helsinki revised in 2013<sup>22</sup>, the European Union Good Pharmacovigilance practices (GVP)<sup>17</sup>, European and National laws in terms of data protection<sup>23</sup> and all current local regulations. Relevant scientific guidelines such as ENCePP Guide on Methodological Standards in Pharmacoeconomics<sup>24</sup> will be considered.

### 15.2 Informed Consent

Due to the retrospective and anonymous nature of data collection for this study, signature of informed consent by patients is not required to abstract data from the patient's chart. A waiver of consent will be requested from IECs.

### 15.3 Institutional Review Board / Independent Ethics Committee Approval

This study is non-interventional. The drug used to treat the patient is based on clinical judgment alone, and, as such, does not come under applicable laws and regulation on clinical trials, as no drug is provided by the Sponsor or any third party. No specific examinations or laboratory tests are to be performed above and beyond those usually undertaken by the investigator, and no additional visits are required for study purposes.

Submissions and/or notification to the appropriate IEC will be performed as required by local legislation in each country for this type of study.

### 15.4 Data Protection

Patients' personal data and investigator's personal data shall be treated in compliance with the European Regulation<sup>23</sup> on the protection of individuals with regard to the processing of personal data and all local applicable laws and regulations.

Data about investigators will be declared to applicable data protection authority and the investigators will be informed – within the framework of the site qualification questionnaire – of their right to access to, rectify or erase data, or their right to restrict or object to processing of the data, as well as the right to data portability.

Patient data will be anonymized, i.e. investigators will not be able to connect the patient with his/her identification number. The sponsor will be blinded to the patient information.

Submission(s) to competent data protection authorities will be performed as appropriate.

### 15.5 Adherence to the Protocol

The study must be conducted as described in the approved protocol. Any significant deviation from the protocol must be reported immediately to the Sponsor and IEC.

## 15.6 Protocol Amendment

Any amendment to the protocol will be created by the Sponsor, and subsequently submitted by the site to the IEC and appropriate regulatory authority for approval.

## 15.7 Retention of Patient Records

When the study is completed, the investigators must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigators will notify the Sponsor prior to moving or destroying any of the study documents.

The Sponsor will maintain the data collected (study database) for at least 5 years.

## 15.8 Confidentiality

The information in this and related documents from the Study Sponsor includes trade secrets and commercial information that are confidential and may not be disclosed, unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted below, is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IEC, or local regulatory agency.

## 16 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY REPORT

The Sponsor and/or designee will develop a final study report after the end of the study. Results will be posted on Clinical Trials.gov.

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. Authorship credit will follow the guidelines established by the International Committee of Medical Journals Editors<sup>25</sup> and, as such, should be based on the following criteria 1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors must meet all above criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above.

## 17 REFERENCES

1. SmPC for Ozurdex. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/001140/WC500095499.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001140/WC500095499.pdf)
2. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)*. 2015 Sep 30;2:17.
3. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, Berrocal MH, Solis-Vivanco A, Farah ME; Pan-American Collaborative Retina Study Group. *Ophthalmology*. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. 2007 Apr;114(4):743-50.
4. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, Boos CJ, Xing W, Egan C, Peto T, Bunce C, Leslie RD, Hykin PG. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*. 2010 Jun;117(6):1078-1086.e2.
5. Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, Eldem B, Monés J, Richard G, Bandello F; European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol*. 2014 Sep;98(9):1144-67.
6. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, Heier JS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Korobelnik JF. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. *Ophthalmology*. 2015 Oct;122(10):2044-52
7. Avery RL, Gordon GM. Systemic Safety of Prolonged Monthly Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema: A Systematic Review and Meta-analysis. *JAMA Ophthalmol*. 2016 Jan; 134(1):21-9.
8. Chen YY, Chang PY, Wang JK. Intravitreal Aflibercept for Patients with Diabetic Macular Edema Refractory to Bevacizumab or Ranibizumab: Analysis of Response to Aflibercept. *Asia Pac J Ophthalmol (Phila)*. 2017 May-Jun; 6(3):250-255.
9. Bhisitkul RB, Campochiaro PA, Shapiro H, Rubio RG. Predictive value in retinal vein occlusions of early versus late or incomplete ranibizumab response defined by optical coherence tomography. *Ophthalmology*. 2013 May; 120(5):1057-63.
10. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol*. 2009 Jan-Feb; 54(1):1-32.
11. Ghanchi F; Diabetic Retinopathy Guidelines Working Group. The Royal College of Ophthalmologists' clinical guidelines for diabetic retinopathy: a summary. *Eye (Lond)*. 2013 Feb; 27(2):285-7.
12. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, Li XY, Cui H, Hashad Y, Whitcup SM; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014 Oct;121(10):1904-14.

13. Mastropasqua R, Toto L, Borrelli E, Di Antonio L, De Nicola C, Mastrocola A, Di Nicola M, Carpineto P. Morphology and Function over a One-Year Follow Up Period after Intravitreal Dexamethasone Implant (Ozurdex) in Patients with Diabetic Macular Edema. *PLoS One*. 2015 Dec 31;10(12):e0145663.
14. ICH Topic E2D - Post Approval Safety Data Management. Note for guidance on definitions and standards for expedited reporting Current Step 5 Version; May 2004.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002807.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002807.pdf)
15. EMA. Guidelines on good pharmacovigilance practices Annex I - Definition. Current Step Rev 4 version 2
16. ICH Topic E2A. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Current Step 5 Version; June 1995.  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002749.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf)
17. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). EMA/873138/2011. Effective date 22 November 2017
18. Querques G, Darvizeh F, Querques L, Capuano V, Bandello F, Souied EH. Assessment of the Real-Life Usage of Intravitreal Dexamethasone Implant in the Treatment of Chronic Diabetic Macular Edema in France. *J Ocul Pharmacol Ther*. 2016 Jul-Aug;32(6):383-9.
19. Escobar-Barranco JJ, Pina-Marín B, Fernández-Bonet M. Dexamethasone Implants in Patients with Naïve or Refractory Diffuse Diabetic Macular Edema. *Ophthalmologica*. 2015;233(3-4):176-85.
20. Iglicki M, Busch C, Zur D, Okada M, Mariussi M, Chhablani JK, Cebeci Z, Fraser-Bell S, Chaikitmongkol V, Couturier A, Giancipoli E, Lupidi M, Rodríguez-Valdés PJ, Rehak M, Fung AT, Goldstein M, Loewenstein A. Dexamethasone Implant for Diabetic Macula Edema in Naïve Compared with Refractor Eyes: The International Retina Group Real-Life 24-Month Multicenter Study. The IRGREL-DEX Study. *Retina*. 2018 Apr 24 [Epub ahead of print]
21. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). Revised June 2015  
[https://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](https://www.pharmacoepi.org/resources/guidelines_08027.cfm)
22. World Medical Association. Declaration of Helsinki. October 2013. <http://www.wma.net/>
23. European Parliament and Council. EU General Data Protection Regulation - Regulation (EU) 2016/679. 27 April 2016. [http://ec.europa.eu/justice/data-protection/reform/files/regulation\\_oj\\_en.pdf](http://ec.europa.eu/justice/data-protection/reform/files/regulation_oj_en.pdf)
24. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Current Revision 3, July 2017.  
[http://www.encepp.eu/standards\\_and\\_guidances/documents/ENCePPGuideofMethStandardsinPE\\_Rev6.pdf](http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev6.pdf)
25. ICMJE. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. December 2016. <http://www.icmje.org/icmje-recommendations.pdf>

## APPENDICES

None