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STUDY TITLE

An Observational, Prospective Post-Marketing Surveillance Program to Evaluate the Safety Profile of Intravitreal Ozurdex® in the Treatment of Visual Impairment Due to Diabetic Macular Edema by Actively Identifying and Evaluating the Occurrence of Adverse Events and Serious Adverse Events Information

Version 1.0, DATE: 09 SEPTEMBER 2016

Protocol Number: 1491-401-008

Emergency Telephone Number:

Serious Adverse Event Reporting Fax Number(s):

Serious Adverse Event Reporting e-mail address:

Allergan Medical Safety Physician:

Contact Information:

Post-Marketing Surveillance Program Information

Title	An Observational, Prospective Post-Marketing Surveillance Program to Evaluate the Safety Profile of Intravitreal Ozurdex® in the Treatment of Visual Impairment due to Diabetic Macular Edema by Actively Identifying and Evaluating the Occurrence of Adverse Events and Serious Adverse Events information
Protocol version identifier	1.0
Date of last version of protocol	09 September 2016
Active substance	Dexamethasone
Medicinal product	Ozurdex® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the Novadur® solid polymer sustained-release drug delivery system
Product reference	Ozurdex® intravitreal implant
Marketing authorization holder	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612
Research question and objectives	The objective of this PMS program is to evaluate the safety profile of Ozurdex® by actively identifying and evaluating the occurrence of AEs and SAEs for 1 year period in adult Indian patients (≥18 years of age) who will be receiving at least one intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.
Country of study	India
Author	

Marketing authorization holder

Marketing authorization holder (MAH)	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 [redacted]
MAH contact person	[redacted]

Investigator Signature Page

An Observational, Prospective Post-Marketing Surveillance Program to Evaluate the Safety Profile of Intravitreal Ozurdex® in the Treatment of Visual Impairment due to Diabetic Macular Edema by Actively Identifying and Evaluating the Occurrence of Adverse Events and Serious Adverse Events information

Post-Marketing Surveillance Program of Intravitreal Ozurdex®

I have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to participate in this study. My signature confirms my agreement that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, Good Pharmacoepidemiology Practices (GPP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this protocol will need to be approved by an Institutional Ethics Committee (IEC), where applicable prior to any subjects being enrolled and that I am responsible for verifying whether that requirement is met. I agree to obtain written informed consent from each of the subject before protocol specified procedures are carried out. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

Print Name

Signature **Date**

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1. Table of contents

2. List of abbreviations

ADR	adverse drug reaction
AE	adverse event
BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRVO	central retinal vein occlusion
DME	diabetic macular edema
DOH	Declaration of Helsinki
GPP	Good Pharmacoepidemiology Practice
ICF	informed consent form
IEC	institutional ethics committee
LLOQ	lower limit of quantitation
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PMS	post-marketing surveillance
PSO	patient safety operations
SAE	serious adverse events
VEGF	vascular endothelial growth factor

3. Responsible parties

Name	Address
Contract Research Organization:	
Point of contact from MAH	

4. Abstract

Study Title: An Observational, Prospective Post-Marketing Surveillance (PMS) Program to Evaluate the Safety Profile of Intravitreal Ozurdex® in the Treatment of Visual Impairment due to Diabetic Macular Edema (DME) by Actively Identifying and Evaluating the Occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs) Information.

Version 1.0, Date: 09 September 2016

Main Protocol Author:

Rationale and background: Ozurdex® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO); non-infectious uveitis affecting the posterior segment of the eye; and DME. Ozurdex® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the Novadur® solid polymer sustained-release drug delivery system.

India is second to China in having the maximum number of diabetics. This significant proportion of diabetes in India indicates an increase in diabetic retinopathy or DME cases. The increase of such cases is directly proportional to the duration of diabetes.

As a part of Allergan's commitment to the Regulatory Authority of India, this PMS program is planned to be conducted to collect safety information from Indian patients who will be receiving intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

Research question and objectives: The objective of this PMS program is to evaluate the safety profile of Ozurdex® by actively identifying and evaluating the occurrence of AEs and SAEs for 1 year period in adult Indian patients (≥18 years of age) who will be receiving at least one intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

Study design: This is an observational, prospective PMS program to evaluate the safety profile of intravitreal Ozurdex® by actively identifying and evaluating the occurrence of AEs and SAEs information.

On the Visit 1/Baseline visit, an informed consent would be provided to the patients for obtaining their consent to share the collected safety information for research purposes. Following the signature on the informed consent form (ICF), the basic required information will be collected at Visit 1. No study medication will be provided as part of the study as this is a non-interventional study of usual clinical practice. However, the marketed intravitreal Ozurdex® injection could be administered to the patient at the discretion of the treating physician/investigator if he/she considers that the patient would benefit with the injection. The injection can be provided by the physician/investigator either in the same visit when informed consent was signed or in the subsequent visit. The date of the injection will be recorded in the pre-designed case report form (CRF). Patients who do not receive the injection will be replaced. During the subsequent follow-up visits/telephonic contact, the study investigator collects the information pertaining to AEs/SAEs, the dates of AE/SAEs if available, date of the last intravitreal Ozurdex® injection and other details entailing the safety information as mentioned in the pre-designed CRF.

Population: Indian adult patients aged ≥18 years who have a visual impairment due to DME.

Study size: The study is planned for one year duration. Approximately 250 patients are planned to be screened and enrolled into the study from approximately 20 sites across India.

Data analysis: The data collected on the CRF (demographic and other baseline data) will be transferred into a clinical database. For continuous data, number of non-missing records, mean, standard deviation, median, minimum, maximum and the two-sided 95% confidence interval (CI) of the mean will be presented. For categorical data, number of non-missing records and percentages will be presented.

Milestones:

Milestone	**Planned date**
Start of data collection	Q3 2016
End of data collection	Q3 2017
Final report of study results	Q4 2017

5. Amendments and updates

None.

6. Milestones

Milestone	Planned date
Start of data collection	Q3 2016
End of data collection	Q3 2017
Final report of study results	Q4 2017

7. Rationale and background

This study focuses on timely detection and characterization of serious and non-serious adverse events (AEs) including important identified and potential risks and AEs of special interest observed with intravitreal Ozurdex® injection for the treatment of visual impairment due to diabetic macular edema (DME) in the Indian population during usual clinical practice.

Ozurdex® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO); non-infectious uveitis affecting the posterior segment of the eye; and DME. Ozurdex® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the Novadur® solid polymer sustained-release drug delivery system[1].

Diabetic macular edema

Diabetic eye disease (retinopathy) can damage the small blood vessels of the eye. Fluid leaking from these blood vessels may cause the central part of the retina (the macula) to swell. This is called DME. Diabetic macular edema is the most common cause of vision loss in people who have diabetes[2]. Diabetic macular edema affects 20% of patients with diabetic retinopathy[3]. Diabetic macular edema is characterized by capillary leakage, fluid accumulation, and macular thickening following breakdown of the blood retinal barrier[4]. Inflammation plays a significant role in DME pathogenesis because the breakdown of the blood retinal barrier involves expression of inflammatory factors[5] including vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1, interleukin-6, monocyte chemotactic protein-1, leukostasis[6] and alterations in endothelial tight junction proteins[7].

India is second to China in having the maximum number of diabetics[8]. The International Diabetes Federation projects the increase in number of people with diabetes in India from 65.1 million in 2013 to 109 million in 2035[9]. This significant proportion of diabetes in India indicates an increase in diabetic retinopathy or DME cases. One risk factor for the development of diabetic retinopathy is hypertension associated with diabetes. The increase of such cases is directly proportional to the duration of diabetes. Proliferative diabetic retinopathy was seen in patients with 11 years of diabetes. Severe diabetic retinopathies were observed in 100% of patients with 25 years of diabetes[10].

Laser photocoagulation, considered for a long time as the main treatment option for DME, may lead to paracentral deficits of the visual field and reduced color vision and sensitivity to contrast[11]. For these reasons, intravitreal therapies with anti-VEGF have been considered as an efficient treatment strategy for patients affected by DME[12]. Intravitreal corticosteroids may be useful in the treatment of DME because they block production of VEGF and other inflammatory mediators[13], inhibit leukostasis[14], and enhance the barrier function of vascular endothelial cell tight junctions[15].

Ozurdex® produces significant improvements in best-corrected visual acuity (BCVA) and central macular thickness from the third day of implant in patients with DME, and this improvement will be sustained until the third month[16].

Retinal vein occlusion

Ozurdex® is also indicated for the treatment of macular edema following BRVO or CRVO. The efficacy of Ozurdex® for the treatment of macular edema following BRVO or CRVO was assessed in two multicenter, double-masked, randomized, parallel studies. Following a single injection, Ozurdex® demonstrated the following clinical results for the percentage of patients with ≥15 letters of improvement from baseline in BCVA.

In each individual study and in a pooled analysis, time to achieve ≥15 letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with Ozurdex® compared to sham ($p < 0.01$), with Ozurdex®-treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a ≥15 letter (3-line) improvement in BCVA with Ozurdex® occurs within the first two months after implantation in approximately 20% to 30% of subjects. The duration of effect persists approximately one to three months after onset of this effect[1].

Posterior segment uveitis

Ozurdex® is also indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The efficacy of Ozurdex® was assessed in a single, multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye. After a single injection, the percentage of patients reaching a vitreous haze score of 0 (where a score of 0 represents no inflammation) was statistically significantly greater for patients receiving Ozurdex® versus sham at week 8 (primary time point) (47% versus 12%). The percentage of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving Ozurdex® versus 7% for sham at week 8[1].

Mechanism of action

Dexamethasone, a corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.

Pharmacokinetics

Plasma concentrations were obtained from 21 patients with macular edema due to BRVO and CRVO, and 21 patients with DME prior to dosing and at 4 to 5 additional post-dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In retinal vein occlusion and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

No metabolites were observed in an *in-vitro* metabolism study following the incubation of [^{14}C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours.

Rationale of the study

As a part of Allergan's commitment to the Regulatory Authority of India, this post-marketing surveillance (PMS) program is planned to be conducted to collect safety information from Indian patients who will be receiving intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

The important identified risks and important potential risks for Ozurdex® are consistent with the current benefit-risk profile.

8. Research question and objectives

The objective of this PMS program is to evaluate the safety profile of Ozurdex® by actively identifying and evaluating the occurrence of AEs and serious adverse events (SAEs) for 1 year period in adult Indian patients (≥18 years of age) who will be receiving at least one intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

9. Research methods

9.1. Study design

This is an observational, prospective PMS program to evaluate the safety profile of intravitreal Ozurdex® by actively identifying and evaluating the occurrence of AEs and SAEs information.

Investigators will be trained on the conduct of the study by the Clinical Research Associate (CRA).

On the Visit 1/Baseline visit, an informed consent would be provided to the patients for obtaining consent to share the collected safety information for research purposes. No further visits are planned as it is at the discretion of the treating physician/investigator to schedule a follow-up (clinic visit/telephonic contact) with the patients. Refer to Annex 1 for sample informed consent form (ICF).

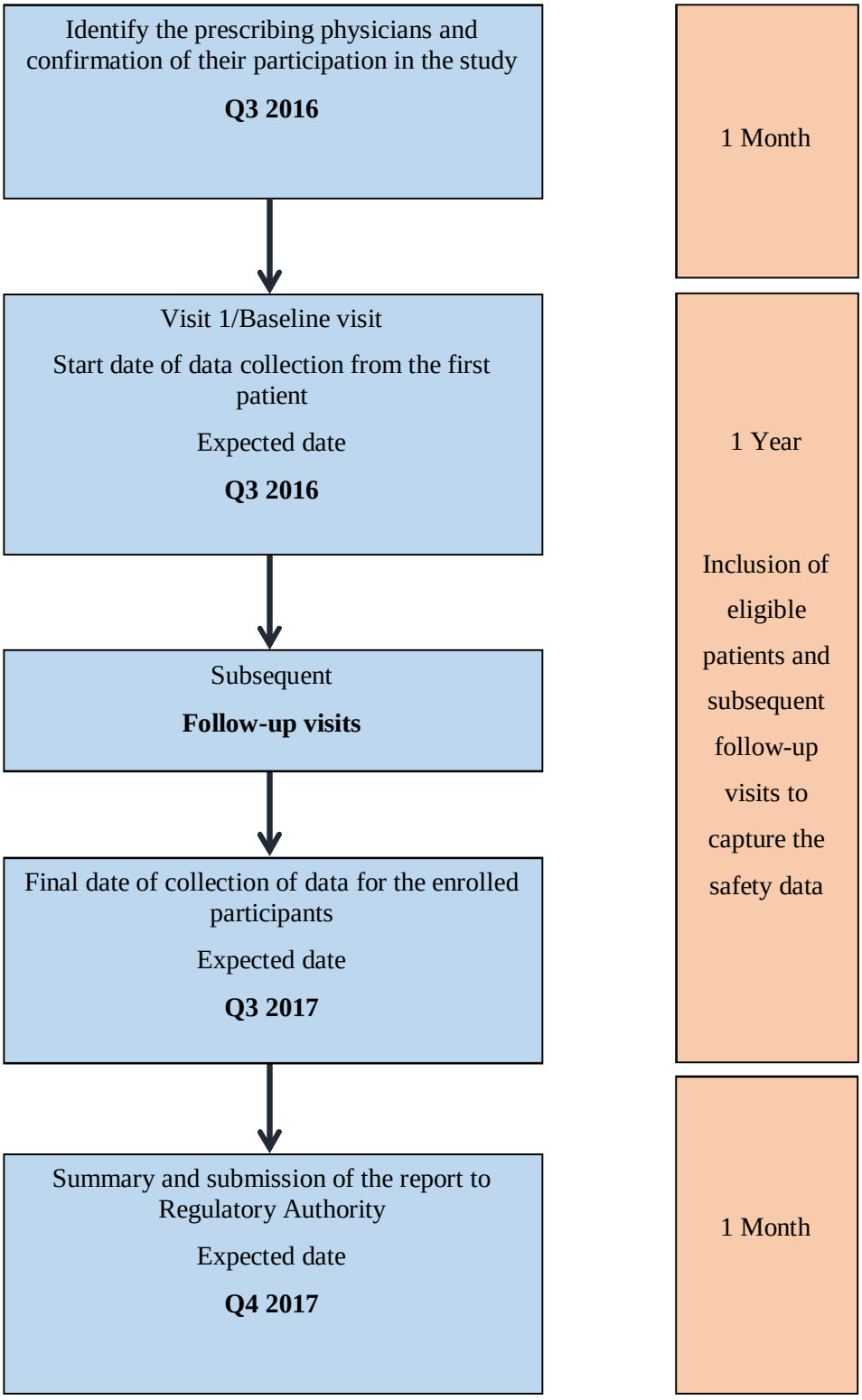
Following the signature on the ICF, the basic required information will be collected at Visit 1 by the study physician in a pre-designed case report form (CRF). The information collected at Visit 1 includes, patient demography characteristics, medical history, concomitant medications, ophthalmic history, concomitant ophthalmic medications, the date of the last intravitreal Ozurdex® injection if applicable, date of the present intravitreal Ozurdex® injection and AEs/SAEs at baseline if any (and the dates of AE/SAEs if available). Refer to Annex 1 for sample CRF.

No medication will be provided as part of the study as this is non-interventional and confers to usual clinical practice. However, the marketed intravitreal Ozurdex® injection could be administered to the patient at the discretion of the treating physician/investigator if he/she considers that it would be beneficial for the patient. The injection can be provided by the physician/investigator either in the same visit when informed consent was signed or in the subsequent visit. The date of the injection given will be recorded. Refer to Annex 1 for the Prescribing Information of Ozurdex® Intravitreal Implant for detailed Ozurdex® administration procedure. Patients who do not receive the injection will be replaced.

During the subsequent follow-up visits/telephonic contact, the study investigator will begin by querying for AEs by asking each subject a general, non-directed question such as “How have you been feeling since the last visit?” Investigator collects the information pertaining to AEs/SAEs and the dates of AE/SAEs if available, date of the last intravitreal Ozurdex® injection and other details entailing the safety information as mentioned in the pre-designed CRF.

For description of the study process, please see Figure 1.

Figure 1: PMS Program Flowchart and Duration of the Program



9.2. Setting

The study is planned for one year duration. No formal calculation of sample size is provided. However, approximately 250 patients are planned to be screened and enrolled into the study from approximately 20 sites across India.

along with Allergan would identify the prescribing physicians strategically located throughout the whole country. Physicians who accept to participate must sign the Investigator Signature Page as an evidence of their approval.

- *Study Visits:* Visit 1/Baseline visit the site collects the following information: Informed consent
- Demography
- Medical history
- Concomitant medications
- Ophthalmic history
- Concomitant ophthalmic medications
- AEs/SAEs/adverse drug reactions (ADRs) (dates if available)
- Information on pregnancy (if applicable)
- Date of the last intravitreal Ozurdex® injection (if available)
- Date of the present intravitreal Ozurdex® injection

The AEs/SAEs/ADRs along with the date of the last intravitreal Ozurdex® injection w.r.t AEs and concomitant medications for the AEs will be collected in subsequent follow-up visits.

Patient Inclusion Criteria

- The patient has signed a written informed consent.
- Adult patient aged ≥18 years.
- The subject who is scheduled to receive at least one intravitreal Ozurdex® injection for the treatment of visual impairment due to DME.

Patient Exclusion Criteria

- Patients for whom Ozurdex is contraindicated:
  - Ocular or periocular infections
  - Glaucoma
  - Torn or ruptured posterior lens capsule
  - Hypersensitivity

9.3. Variables

Study Assessments:

- **Written informed consent:** Information about the program should be given in written form. Subjects, their relatives, guardians, if necessary legal representatives must be given ample opportunity to discuss any details of the program with the study

physician/investigator. Informed consent should be documented and signed by the patient before protocol-specified procedures are carried out.

- **Demography:** The following demographic details will be taken and recorded in the CRF

  Age, Gender, Date of Birth, Height and Weight.

- **Medical history:** Patients' relevant medical history pertaining to diabetes mellitus and its complications will be recorded. The following medical history details will be recorded in the CRF.

  Name of the medical condition, type of the medical condition (if applicable), date of diagnosis of the medical condition, whether the medical condition is being treated or not, whether the medical condition is ongoing or stopped, if stopped, the stop date will be recorded. Any additional information about the complications arising due to diabetes mellitus will also be recorded as medical history.

- **Concomitant medications:** Patients relevant concomitant medications will be recorded. The following concomitant medication details will be recorded in the CRF.

  Name of the concomitant medication, start date of the concomitant medication, whether the concomitant medication is ongoing or stopped, if stopped, the stop date will be recorded, reason for the intake of concomitant medication (indication for use), dose, unit and frequency.

- **Ophthalmic history:** Patients relevant ophthalmic history will be recorded. The following ophthalmic history details will be recorded in the CRF.

  Name of the ophthalmic condition, date of diagnosis of the ophthalmic condition, whether the medical condition is being treated or not, whether the medical condition is ongoing or stopped, if stopped, the stop date will be recorded.

- **Concomitant ophthalmic medications:** Patients relevant concomitant ophthalmic medications will be recorded. The following concomitant ophthalmic medication details will be recorded in the CRF.

  Name of the concomitant ophthalmic medication, start date of the concomitant ophthalmic medication, whether the concomitant ophthalmic medication is ongoing or stopped, if stopped, the stop date will be recorded, reason for the intake of concomitant ophthalmic medication (indication for use), dose, unit and frequency.

- **Information on pregnancy:** The following information will be recorded from the expecting female patients in the CRF at the initial visit.

  Pregnancy status – Pregnant: Yes/No.

  There is no requirement as part of the study to confirm pregnancies by a laboratory test.

  Detailed information on pregnancy will be recorded and sent to Allergan either by fax or email mentioned in the page 1 of protocol by using Allergan pregnancy data communication form – Pre-delivery (initial) information. This form will be filled for all pregnancies in a female study patient or pregnancy in the partner of a male study patient.

During the subsequent visits, detailed information on follow-up (post-delivery) of pregnancy will be recorded and sent to Allergan either by fax or email mentioned in the page 1 of protocol by using Allergan pregnancy data communication form – Post-delivery (follow-up) information.

- **AEs/SAEs/ADRs:** The following details will be recorded in the CRF pertaining to AEs/SAEs/ADRs.

  Verbatim term of the event, onset date of the event, resolution date of the event, seriousness, severity (mild, moderate, severe), outcome of the event, treatment for the event, relationship (related, not related) of the event to intravitreal Ozurdex® injection as judged by the study physician, action taken with respect to Ozurdex® will be recorded. Concomitant medications administered for the corresponding AE with details of start date, stop date, dose, unit and frequency will be captured.

  Information on AEs/SAEs/ADRs will be recorded and sent to Allergan either by fax or email mentioned in the page 1 of protocol by using PMS AE form (SAE and non-serious ADR form).

- **Date of the last intravitreal Ozurdex® injection**: Date of the last dose of intravitreal Ozurdex® injection if available will be recorded.

9.4. Data sources

Medical records of the patient will be used which serves as a data for determining exposures, effects and outcomes. Other variables such as potential confounding variables and effect modifiers will also be collected.

9.5. Study size

No formal sample size calculation is performed since this is an observational, prospective, non-interventional study without a comparison group and the goal is to evaluate the usual clinical practice experience with Ozurdex® in all the eligible patients. Approximately 250 patients are planned to be enrolled into the study from 20 sites across India based on the enrollment potential and is considered a representative sample.

9.6. Data management

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation. Concurrent manual data review will be performed based on parameters dictated by the plan.

Paper-based CRF will be used to collect the data from the sites. Refer to Annex 1 for sample CRF.

9.7. Data analysis

The data collected on the CRF (demographic and other baseline data) will be transferred into a clinical database.

For continuous data, number of non-missing records, mean, standard deviation, median, minimum, maximum and the two-sided 95% confidence interval (CI) of the mean will be presented. For categorical data, number of non-missing records and percentages will be presented.

Patients who do not return for follow-up will not be replaced and will be treated as censored. Missing data will be censored and no imputation will be performed.

Frequency of AE/SAEs among the study participants during the study period will be calculated if applicable.

Concomitant medications entered into the database will be coded using the World Health Organization Drug Reference. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

9.8. Quality control

Site Qualification visits will be performed by a CRA from along with a representative from Allergan. During the site initiation visit, the CRA will provide face to face training on the conduct of the study to the participating physician. The CRA will remotely manage this study and the details on Remote Site Management will be described in study specific plans. The CRA will remotely closeout each site after the last patient's final follow-up assessment is completed and all CRF data has been entered and retrieved and all outstanding issues at the site have been resolved or addressed. In the case where a site is closed before completion of the study, the site will communicate to the Institutional Ethics Committee (IEC) of the same and the CRA will remotely close out the site but will maintain contact with the physician regarding the study status and in case follow-up information is required.

9.9. Limitations of the research methods

This is an observational study aimed to collect and evaluate only the safety data. There is no hypothesis testing in the study to evaluate any statistical significance. Frequency of AE/SAEs will be calculated as appropriate. This is a single arm study where no comparisons are possible to assess causality. Incident and pre-existing safety event may not be able to be differentiated if the date of occurrence is not available. Information from this study would supplement safety data already available and is part of the regulatory commitment. As there is no study mandated visits or procedures, missing data could be observed to a large extent.

9.10. Other aspects

9.10.1 Source documents

The physician should maintain source documents for each patient enrolled in the study. Source documents such as patient charts and doctors' notes will be kept as part of the patients' medical records. Patient files including medical records and signed patient ICFs must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after completion of the study.

9.10.2 File retention and archiving

The physician at the study sites will maintain a record of each enrolled patient. Physicians will be instructed on source documentation that must be available to substantiate patient identification, eligibility and participation, proper informed consent procedures, dates of data collection, adequate reporting and follow-up of AEs, concomitant medication, and drug administration.

10. Protection of human subjects

Intravitreal Ozurdex® injection is marketed for various other indications as mentioned in the Prescribing Information[1]. There are no additional anticipated risks to the patients with this product.

The confidentiality of records, notifications, contact details, databases and any other information generated during the study that could reveal the identity of patients will be guaranteed, respecting the privacy and in compliance with country requirements. All information related to this study is considered confidential and remains as exclusive property of Allergan.

11. Management and reporting of adverse events/adverse reactions

11.1. Definitions

Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that 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 (investigational) product, whether or not considered related to the medicinal (investigational) product. This includes but is not limited to AEs which arise from:

- the use of a medicinal product within the terms of the marketing authorization;
- the use outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.

Note: AEs must be collected once informed consent has been obtained, regardless of whether or not the subject has been administered study drug. Patients who do not receive the injection will be replaced.

Serious adverse event

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Allergan considers all cancer AEs as SAEs. In addition, an abortion (spontaneous or non-spontaneous) is also considered an SAE.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a subject requires hospitalization is not reportable as an SAE.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the subject’s entry into the study. If it has not been documented at the time of the subject’s entry into the study, then it should be documented as an SAE and reported to Allergan.

Adverse drug reaction

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

Severity of AE

A clinical determination will be made of the intensity of an AE. The severity assessment for an AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.

All AEs/SAEs/ADRs that occur during and/or after administration of the product during the follow-up period will be collected regardless of causal relationship to the product.

All AEs, SAEs and ADRs (serious or not) should be recorded on the study CRF. All AEs, SAEs and ADRs should be reported to Allergan global safety team at

Each participating investigator will be trained on the recording of AEs/SAEs/ADRs. The physician or site staff should instruct patients to report SAEs and reportable AEs from the time of enrollment through end of follow-up or early discontinuation from the study during this time period.

Reporting of the events:

Each patient interview will begin with simple open-ended questions and questions designed to collect information regarding specific outcomes of interest. If a patient is seen by a non-study physician, the study physician and/or trained site staff should make every effort to follow-up with the relevant concerned health care provider to obtain all information necessary for the accurate reporting of the event in a timely manner.

All AEs, SAEs and ADRs (serious or not) should be recorded on the study CRF. All events reported on the CRF by the study physician will be confirmed by medical record review and/or direct follow-up with the treating physician. In the event of a death, cause of death will be recorded.

Since this is a non-interventional study, the following types of events should be sent to Allergan global safety team: AEs, SAEs, non-serious ADRs, pregnancies and special situations (lack of effect, overdose, medication error, misuse, abuse, off-label use, use while breastfeeding or occupational exposure).

Pregnancy and all SAEs are to be sent **within 24 hours** of awareness of the event either directly from the site to patient safety operations (PSO) by emailing [redacted] or faxing (primary [redacted]; back-up [redacted]) within 24 hours of the receipt date (or as soon as possible, but no later than 24 hours for death or life-threatening reports) to PSO. The site should also inform [redacted] in parallel. See below for reporting pregnancies.

Similarly, non-serious AEs, non-serious ADRs and special situations should be reported by the site **within 10 calendar days** of receipt to PSO.

To report the SAEs, non-serious AEs, non-serious ADRs and special situations, the site representative completes the SAE and Non-Serious ADR Form (GSE-SIMR-F-041) and sends directly to Allergan PSO along with the fax cover sheet by emailing [redacted] or faxing (primary [redacted]; back-up [redacted]) within their reportable timeframe as discussed above.

To report the pregnancies, Allergan pregnancy data communication forms (pre-delivery GSE-SIMR-F-005; post-delivery GSE-SIMR-F-006) should be used to report in a similar manner. The site should also inform [redacted] in parallel.

If additional information is required, PSO will make this request by emailing the site. The site representative should provide the requested follow-up information to the PSO in writing either by fax or via e-mail attachment. The site should also inform [redacted] in parallel.

Site will promptly inform the governing IEC of the SAE as required by the IEC.

Being a post marketing surveillance study, the AE or SAE reporting to governing health authority will follow the regulations applicable for a marketed product that is, all cases involving serious unexpected adverse reactions shall be reported to the licensing authority by Allergan within 15 days of initial receipt of the information and other non-serious AEs will be reported through Periodic Safety Update Report that follows the prescribed periodicity.

12. Plans for disseminating and communicating study results

12.1. Study reports

Reports	Reporting Period	Data Lock Point	Planned submission date
End of one year from study initiation Final report submitted to agency for further subject expert committee evaluation.	DD Month YYYY - DD Month YYYY	DD Month YYYY	Q4 2017

12.2. Publications of study results

Allergan as the Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

13. References

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Annex 1. List of stand-alone documents

Number	Form number	Title
1.	NA	Prescribing Information of Ozurdex® Intravitreal Implant
2.	NA	List of investigators/sites
3.	NA	Sample Informed Consent Form and Patient Information Form
4.	NA	Sample CRF
5.	GSE-SIMR-F-005	Allergan pregnancy data communication form – Pre-delivery (initial) information.
6.	GSE-SIMR-F-006	Allergan pregnancy data communication form – Post-delivery (follow-up) information.
7.	GSE-SIMR-F-041	Sample PMS AE Form (serious adverse event and non-serious adverse drug reaction form)
8.	NA	Good Pharmacoepidemiology Practices (GPP)
9.	NA	Declaration of Helsinki(DOH)