PASS Information

Title	Evaluation of the Physician Education Component of the Ozurdex Risk Management Plan
Protocol version identifier	Version 3.0
Date of last version of protocol	15 March 2018
EU PAS Register number	The study will be registered prior to data collection.
Active substance	Dexamethasone (ATC code:
Medicinal product	Ozurdex
Product reference	
Procedure number	
Marketing authorisation holder(s)	Allergan Pharmaceuticals Ireland
Joint PASS	No
Research question and objectives	The primary objective of this survey is to assess the effectiveness of the educational material provided to physicians treating patients with Ozurdex by evaluating the physicians' knowledge and understanding of the key information in the Ozurdex Injector's Guide. Specifically, the survey will assess physician knowledge and understanding of the following: ▪ Preparation of the Ozurdex delivery system ▪ Proper Ozurdex intravitreal injection procedure ▪ Proper monitoring of patients after Ozurdex injection ▪ Knowledge of risks and adverse events associated with Ozurdex In addition, the survey will evaluate physicians' knowledge of key safety aspects outlined in the Ozurdex summary of product characteristics (SmPC) (e.g., contraindications and precautions for Ozurdex use). The questionnaire will also investigate whether physicians have received the Ozurdex Injector's Guide and assess the usefulness of the guide.
Country(-ies) of study	France, Germany, Spain, United Kingdom
Author	

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Allergan Pharmaceuticals Ireland Castlebar Road Westport, Co Mayo Ireland
MAH contact person	[redacted]

Approval Page,

Project Title: Evaluation of the Physician Education Component of the Ozurdex Risk Management Plan

Protocol ID Number: CMO-EPI-EYE-0522

Effective Date: 15 March 2018

Authors:

Version: 3.0

The following people have reviewed the protocol and give their approval:

Approval Page, Allergan

Project Title: Evaluation of the Physician Education Component of the Ozurdex Risk Management Plan

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The following people have reviewed the protocol and give their approval:

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2 List of Abbreviations

AE	adverse event
EDC	electronic data capture
EU	European Union
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MAH	marketing authorisation holder
OQA	Office of Quality Assurance
PAS	post-authorisation study
PASS	post-authorisation safety study
RMP	risk management plan
SmPC	summary of product characteristics
TBD	To be determined

3 Responsible Parties

an independent, non-profit research organisation, developed this protocol in collaboration with Allergan and is responsible for the design, conduct, analysis, and reporting of the study.

Surveys and Observational Studies
, Project Management
, Statistician
Senior Director, Data Management

Epidemiology

Allergan is the sponsor of the study. Allergan is responsible for fulfilling any responsibilities for reporting results to regulatory agencies.

Allergan Ireland Castlebar Road, Westport, County Mayo, Ireland

4 Abstract

Title: Evaluation of the Physician Education Component of the Ozurdex Risk Management Plan

Version and Date: 3.0, 15 March 2018
Authors:

Rationale and background: Ozurdex is a dexamethasone intravitreal implant indicated for the treatment of macular oedema following branch retinal vein occlusion or central retinal vein occlusion, the treatment of diabetic macular oedema in patients who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy, and for the treatment of non-infectious uveitis affecting the posterior segment of the eye. Dexamethasone, a potent anti-inflammatory corticosteroid, is contained within a biodegradable implant and delivered via a single-use intravitreal injection device. It provides rapid and sustained improvement in visual acuity that can last up to 6 months.

The European Commission first granted a marketing authorisation, valid throughout the European Union (EU), for the treatment of macular oedema secondary to branch retinal vein occlusion and central retinal vein occlusion on 27 July 2010. The marketing authorisation was extended to include posterior non-infectious uveitis on 16 June 2011 and to include diabetic macular oedema on 26 August 2014.

Ozurdex has a risk management plan (RMP) in place as a condition of market authorisation in the EU, the goal of which is to minimise risk and maximise benefit. As described in the Ozurdex RMP, the important identified risks include: glaucoma, ocular hypertension, increased intraocular pressure, cataract formation and associated visual acuity reduced, vitreous detachment or haemorrhage, endophthalmitis, retinal tear/detachment, significant vitreous leak or hypotony, device dislocation, implant misplacement, and retinitis secondary to reactivation of latent viral or other ophthalmic infections.

As part of the RMP for Ozurdex, Allergan developed and distributed a physician information package to all Ozurdex prescribers to instruct prescribers on the recommended injection technique and to communicate the important risks associated with Ozurdex. Allergan subsequently conducted a physician survey from 2013 November to 2014 January to assess the effectiveness of the physician information component of the educational materials. Based on the results of that survey and per a request from the European Medicines Agency, Allergan revised the Ozurdex educational materials. The revised physician information package includes the following documents: An Injector's Guide to OZURDEX® and A patient guide to OZURDEX® therapy. Allergan distributed these revised materials to physicians beginning in 2014, and distribution is ongoing.

Allergan has collaborated with to develop an observational post-authorisation safety study to assess physician knowledge and understanding of the key safety information in the revised educational material developed by Allergan.

Research question and objectives: The primary objective of this survey is to assess the effectiveness of the educational material provided to physicians treating patients with Ozurdex by evaluating the physicians' knowledge and understanding of the key

information in the Ozurdex Injector's Guide. Specifically, the survey will assess physician knowledge and understanding of the following:

- Preparation of the Ozurdex delivery system
- Proper Ozurdex intravitreal injection procedure
- Proper monitoring of patients after Ozurdex injection
- Knowledge of risks and adverse events associated with Ozurdex

In addition, the survey will evaluate physicians' knowledge of key safety aspects outlined in the Ozurdex summary of product characteristics (SmPC) (e.g., contraindications and precautions for Ozurdex use). The questionnaire will also investigate whether physicians have received the Ozurdex Injector's Guide and assess the usefulness of the guide.

Study design: The study, which will involve up to four European countries, will be an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour among a sample of physicians with recent Ozurdex experience.

The study will include two sampling sources for recruitment: physician lists provided by Allergan and physician panels. In countries where physician lists are available for the study (currently Germany and the United Kingdom [UK]), all physicians on the lists with valid contact information will be recruited for participation. In addition, physicians will be invited using a random sample of physicians (ophthalmologists and retinal specialists) from physician panels. Physicians will be recruited with the aim of obtaining a sample generally representative of physicians who have administered Ozurdex in the selected countries. Depending on what contact information is available, invitations will be sent via e-mail and/or regular mail and/or made by phone to the selected physicians, inviting them to participate and providing a link to a web-based questionnaire. After giving consent, physicians will be asked to complete the questionnaire to evaluate their knowledge and understanding of key safety information, as well as their receipt and use of the Ozurdex Injector's Guide. Once the protocol and questionnaire are approved by the European Medicines Agency (EMA), physician recruitment and data collection will be initiated and will continue for approximately 3 months. Data collection will be monitored closely to determine the number of completed questionnaires in each country. Extending the data-collection period may be considered if it is necessary to allow more time for recruitment efforts.

Population: The study population will include ophthalmologists and retinal specialists in France, Germany, Spain, and the UK who have administered an Ozurdex injection to at least one patient in the past 6 months.

Physicians who participated in the cognitive interviews will be excluded from participating in the study.

Variables: The questionnaire will contain questions eliciting responses that measure knowledge and understanding of the key information in the Ozurdex Physician Injector's Guide and the SmPC.

Data sources: The source of information for the study will be self-reported data collected using a standard questionnaire with closed-ended response choices.

The questionnaire was cognitively tested through interviews with physicians with Ozurdex experience to ensure cultural appropriateness and to improve the ease with

which the questionnaire is understood and completed. The questionnaire was revised subsequent to the interviews based on physician feedback.

Study size: The study will target 75 to 100 completed physician surveys per country, for a total of 300 to 400.

Data analysis: The analyses will be descriptive in nature and will include a detailed review of responses to individual questions, as well as potential summary measure across logical groupings of response items. Results will be stratified by logical variables, such as experience with Ozurdex. A detailed analysis plan describing methods of analysis and presentation and including table shells will be developed before analysis of data is initiated.

Milestones:

- Regulatory approval of protocol and physician questionnaire - Q2 2018
- Institutional review board review and exemption - 22 June 2017
- Ethics Committee reviews - Q3 2018 (if required)
- Health Authority notifications - Q2 2018
- Registration in the EU Post-Authorisation Study Register - Q2 2018
- Data collection - Q2 to Q3 2018
- Final report of study results - Q1 2019

5 Amendments and Updates

None to date.

6 Milestones

Milestone	Anticipated / Actual Timelines
Regulatory approval of protocol and physician questionnaire	Q2 2018
Institutional review board (IRB) review and exemption	22 June 2017
Ethics committee (EC) reviews	Q3 2018 (if required)
Health authority (HA) notifications (as needed)	Q2 2018
Registration in the EU PAS Register	Q2 2018
Start of data collection	Q2 2018
End of data collection	Q3 2018
Final report of study results	Q1 2019

EU = European Union; IRB = Institutional Review Board; PAS = post-authorisation study

7 Rationale and Background

Ozurdex is a dexamethasone intravitreal implant indicated for the treatment of macular oedema following branch retinal vein occlusion or central retinal vein occlusion, the treatment of diabetic macular oedema in patients who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy, and for the treatment of non-infectious uveitis affecting the posterior segment of the eye. Dexamethasone, a potent anti-inflammatory corticosteroid, is contained within a biodegradable implant and delivered via a single-use intravitreal injection device. It provides rapid and sustained improvement in visual acuity that can last up to 6 months (Ozurdex summary of product characteristics, 2016).

The European Commission first granted a marketing authorisation, valid throughout the European Union (EU), for the treatment of macular oedema secondary to branch retinal vein occlusion and central retinal vein occlusion on 27 July 2010. The marketing authorisation was extended to include posterior non-infectious uveitis on 16 June 2011 and to include diabetic macular oedema on 26 August 2014.

Ozurdex has a risk management plan (RMP) in place as a condition of market authorisation in the EU, the goal of which is to minimise risk and maximise benefit. As described in the Ozurdex RMP, the important identified risks include glaucoma, ocular hypertension, increased intraocular pressure, cataract formation and associated visual acuity reduced, vitreous detachment or haemorrhage, endophthalmitis, retinal tear/detachment, significant vitreous leak or hypotony, device dislocation, implant misplacement, and retinitis secondary to reactivation of latent viral or other ophthalmic infections. In controlled Ozurdex studies, the most common adverse reactions reported by $\geq$ 20% of patients were increased intraocular pressure and conjunctival haemorrhage. The important potential risk described in the RMP is systemic corticosteroid effects.

As part of the RMP for Ozurdex, Allergan developed and distributed a physician information pack to all Ozurdex prescribers to instruct prescribers on the recommended injection technique and to communicate the important risks associated with Ozurdex. Allergan subsequently conducted a physician survey from 2013 November to 2014 January to assess the effectiveness of the physician information component of the educational materials. Based on the results of that survey and per a request from the EMA, Allergan revised the Ozurdex educational materials. The revised physician information package includes the following documents: An Injector's Guide to OZURDEX® and A patient guide to OZURDEX® therapy. Key content of the materials includes recommended injection technique, key signs and symptoms of injection-related adverse events (AEs), patient monitoring, and proper management of AEs. Allergan distributed these revised materials via the sales representatives to physicians in each country beginning in 2014, and distribution is ongoing. This study aims to evaluate the effectiveness of the risk minimization measures after 4 years of physicians gaining experience with administration of Ozurdex. As described by this protocol, Allergan has collaborated with [redacted] to develop an observational post-authorisation safety study to assess physician knowledge and understanding of the key safety information in the revised educational material developed by Allergan.

8 Research Question and Objectives

The primary objective of this survey is to assess the effectiveness of the educational material provided to physicians treating patients with Ozurdex by evaluating the physicians' knowledge and understanding of the key information in the Ozurdex Injector's Guide. Specifically, the survey will assess physician knowledge and understanding of the following:

- Preparation of the Ozurdex delivery system
- Proper Ozurdex intravitreal injection procedure
- Proper monitoring of patients after Ozurdex injection
- Knowledge of risks and AEs associated with Ozurdex

In addition, the survey will evaluate physicians' knowledge of key safety aspects outlined in the Ozurdex summary of product characteristics (SmPC) (e.g., contraindications and precautions for Ozurdex use). The questionnaire will also investigate whether physicians have received the Ozurdex Injector's Guide and assess the usefulness of the guide.

9 Research Methods

9.1 Study Design

The study, which will involve up to four European countries, will be an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour among a sample of physicians with recent Ozurdex experience.

In countries where physician lists are available for the study (currently Germany and the UK), all physicians on the lists with valid contact information will be recruited for participation. In addition, physicians will be invited using a random sample of physicians (ophthalmologists and retinal specialists) from physician panels. Physicians will be recruited with the aim of obtaining a sample generally representative of physicians who have administered Ozurdex in the selected countries. Depending on what contact information is available, invitations will be sent via e-mail and/or regular mail and/or made by phone to the selected physicians, inviting them to participate and providing a link to a web-based questionnaire. After giving consent, physicians will be asked to complete a one-time questionnaire to evaluate their knowledge and understanding of key safety information, as well as their receipt and use of the Ozurdex educational materials. Once the protocol and questionnaire are approved by the EMA, physician recruitment and data collection will be initiated and will continue for approximately 3 months. Data collection will be monitored closely to determine the number of completed questionnaires in each country. Extending the data-collection period may be considered if it is necessary to allow more time for recruitment efforts.

Data from the questionnaire responses will be analysed to estimate the level of knowledge, understanding, and reported safe use practices among these physicians stratified by country and other relevant characteristics (e.g., number of prior injections).

9.2 Setting

This cross-sectional study will be conducted in each of four western European countries (France, Germany, Spain, and the UK). Four countries are included to provide some diversity in practice patterns and to observe physician knowledge in different settings, which will maximize the generalizability of the study. In addition, it is anticipated that the drug utilisation in these countries will provide a sufficient number of eligible physicians with Ozurdex experience to participate in the study. A brief, informal feasibility assessment was performed, and the results suggested that recruitment efforts would yield a sufficient number of eligible physicians to meet target sample sizes in each country, with the possible exception of Germany.

9.2.1 Physician Selection

The study will include two sampling sources for recruitment: physician lists provided by Allergan and physician panels. In countries where physician lists are available for the study (currently Germany and the UK), all physicians on the lists with valid contact information will be recruited for participation. The physician lists are comprised of ophthalmologists who have prescribed or will potentially prescribe Ozurdex. The lists include available contact information that can be found in the public domain obtained from internal Allergan sources.

In addition, physicians will be recruited by selecting a random sample of physicians from online physician panels made up of convenience samples of physicians derived from multiple sources (e.g., individual opt-ins, hospital books, medical directories, peer referrals). In countries where a physician list is not available for the study, the physician panels will serve as the sole source for recruitment.

Physicians will be recruited with the aim of obtaining a sample generally representative of physicians who have administered Ozurdex in the selected countries. Follow-up reminders will be sent as needed to physicians who have not accessed the link or completed the survey to achieve the targeted sample size in each country.

9.2.2 Physician Eligibility

The study population will include ophthalmologists and retinal specialists in France, Germany, Spain, and the UK who have administered an Ozurdex injection to at least one patient in the past 6 months.

Physicians who participated in the cognitive interviews will be excluded from participating in the study.

9.3 Variables

The physician questionnaire will be based on the version of the educational and informational materials available at the time of questionnaire development and will

contain closed-ended questions (e.g., multiple choice, true/false), with no free-text response fields.

The questionnaire will collect information related to physician characteristics and experience with Ozurdex, as well as questions to assess physicians' knowledge and understanding of proper injection technique and the risks associated with intravitreal injection with Ozurdex. Specifically, Table 1 outlines the key safety information to be evaluated along with the corresponding items to be included in the draft questionnaire.

Table 1. Key Safety Information and Corresponding Questionnaire Items

Key Safety Information	Data Source	Questionnaire Items
Contraindications for Ozurdex injection	SmPC	6
Patient preparation for injection with Ozurdex	Injector's Guide	7
Proper injection technique	Injector's Guide	8-14
Important risks associated with Ozurdex injection	Injector's Guide	15, 16
Patient monitoring after injection	Injector's Guide	17-20
Importance of counselling patients on symptom reporting	Injector's Guide	21

In addition, the questionnaire will include items to investigate physician receipt and use of the Ozurdex Injector's Guide.

The physician questionnaire is included in Annex 3.

9.4 Data Sources

Sources for the study will include data collected from physicians using a standard questionnaire with closed-ended response choices. The questionnaire has been developed using best practices for instrument development. The questions have been tailored to the study aims and the information provided in the Ozurdex Injector's Guide and SmPC. Other questions will gather information needed to describe the participants, assess potential differences across subgroups, and identify any biases (e.g., demographics, experience administering Ozurdex).

To thoroughly evaluate the questionnaire before fielding the study, the questionnaire has been tested through cognitive interviews with 5 physicians in each country who prescribe and/or administer Ozurdex to ensure that the introductory text, consent form, and questionnaire items (question stems and response choices) are culturally appropriate and easily and correctly understood in the local language by individuals similar to those who will participate in the full survey. The questionnaire was subsequently revised based on feedback from the physician interviews in each country. Physicians who participated in the cognitive interviews will be excluded from participating in the study.

Cognitive pretest interviewing is a well-established qualitative research methodology used to identify problems with questionnaire items and response options (Groves et al., 2009). Specifically, trained interviewers ask pretest interview participants to complete the questionnaire while thinking aloud or describing their thought processes as they answer the questionnaire items. Pretest interviewers use an interview guide that includes probe questions designed to help interviewers understand how each participant interpreted and chose his or her answers for each item in the draft questionnaire. The

pretest interviews are designed to help identify problems with questionnaire items including the question stems and response choices and to ensure that participants understand the instructions. The pretest interview data were used to optimise the language used in the questionnaire prior to fielding the survey. Likewise, the cognitive pretest interviews helped identify cultural or translational issues with the draft questionnaire so that it could be modified to meet the individual needs of each country while maintaining comparability across the study.

9.5 Study Size

The study will target 75 to 100 completed physician surveys per country, for a total of 300 to 400, to allow for reasonable precision around estimates of the physicians' knowledge and comprehension levels by country and overall. For example, using the assumption that the sample of participating physicians can be treated as a simple random sample and that the expected percentage of correct responses to a true/false question is 80%, then for a sample size of 400, the lower bound of the exact 95% confidence interval would be 75.7%, and the upper bound would be 83.8%. Smaller sample sizes will yield less precise estimates; nevertheless, the desire for precision needs to be balanced by the total pool of potentially available participants. Furthermore, larger sample sizes do not necessarily result in substantial gains in precision. 0 shows the expected exact 95% confidence limits when assuming various combinations of sample size and levels of correct responses.

Table 2. Exact 95% Confidence Limits for Various Combinations of Study Size and Correct Response Percentage

Physician Sample Size	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
75	80	69.2	88.4
75	85	74.9	92.2
100	80	70.8	87.3
100	85	76.5	91.4
300	80	75.0	84.4
300	85	80.4	88.8
400	80	75.7	83.8
400	85	81.1	88.4

9.6 Data Collection

A web-based electronic data capture (EDC) system will be used in this study.

Invitations will be sent via e-mail and/or regular mail and/or made by phone to the selected physicians, inviting them to participate and providing a link to the web-based questionnaire. During the data collection period, invitations will be sent to each sampled physician approximately three times to boost response and encourage timely completion of the survey.

Each invited physician will be asked to log in to the study website by entering a unique identification number and password assigned to each physician and provided in the invitation to participate. The questionnaire will begin with informed consent. After physicians' consent, they will be prompted to complete the questionnaire. A screening question will be included at the beginning of the questionnaire to confirm that the physician has administered an Ozurdex injection at least once within the past 6 months.

The questionnaire will be self-administered (with closed-ended questions with predefined answers) and can be completed at the physicians' convenience. Although physicians will be encouraged to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and, at a later time while the survey

is still open (i.e., during the data-collection period), pick up where they left off, should that be necessary. Physicians will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the participants searching for answers via the web or other sources or being influenced by answers to subsequent questions.

Physicians will also not be allowed to regain access to the questionnaire once they have submitted it. Based on potential country-specific requirements, the recruitment process (e.g., use of e-mail, regular mail, and/or phone) and physician questionnaire content may be slightly different between countries. Country-specific differences, if any, will be described and appended to the final study protocol.

Once the protocol and questionnaire are approved by the EMA, physician recruitment and data collection will be initiated and continue for approximately 3 months. Extending the data-collection period may be considered if it is necessary to allow more time for recruitment efforts.

9.7 Data Management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will describe, if necessary, country-specific modifications due to local regulations or requirements.

Physicians will enter data directly into a web-based EDC system. Edit and logic checks will be specified in a data cleaning specifications document and will be programmed into the web-based EDC system to ensure high-quality data. However, due to the self-reported nature of the data, changes to data that appear to be incorrect or inconsistent during data cleaning may not be possible.

data managers will conduct user acceptance testing of the web-based EDC system and will sign the user acceptance testing report before the EDC system is used in the field. Additionally, data managers will approve the data management plan, the annotated physician questionnaire, the data cleaning specifications document, and the testing summary reports before authorising the data systems to go “live.” Data managers will ensure that the EDC system remains tested and valid and will require that testing documentation, database documentation, and change control documentation will be created and maintained.

Once the web-based EDC system is in the field, data management activities will include review of interim analysis files for consistency, programming edit checks in preparation for statistical analysis, and merging data sets if required.

9.7.1 Record Retention

All data for the physician survey will be electronic. Responses to the survey will be collected and stored in the United States by the panel provider), which maintains a privacy shield certification. Only deidentified data based on case identification numbers will be shared with in the United States for the purpose of analysis and generation of the final report. The deidentified electronic data sets will be provided to Allergan at the end of the study, in which case Allergan will be responsible for long-term storage of the data.

9.8 Data Analysis

A detailed analysis plan describing methods of analysis and presentation and including table shells will be developed prior to starting analysis of data. The analyses will be descriptive in nature and will include detailed review of responses to individual questions and potential summary measures across logical grouping of response items.

Descriptive tables will be generated for the physicians overall, stratified by country and other identified variables of interest. Questionnaire items will be divided into the logical groupings for analysis. 0 provides an example of these categories.

Table 3. Example Analysis Tables

Analysis Table	Questionnaire Items
Physicians' experience with Ozurdex	3-5
Physicians' knowledge of key safety information	
▪ Contraindications for Ozurdex injection	6
▪ Patient preparation for injection with Ozurdex	7
▪ Proper injection technique	8-14
▪ Important risks associated with Ozurdex injection	15, 16
▪ Patient monitoring and counselling	17-21
Physician receipt, review, and ratings of the Ozurdex Injector's Guide	22-24
Physician characteristics	25-27

Analysis tables will include the frequency and percentage of physicians who select each response to each individual question. In addition, for knowledge questions with multiple correct responses, derived variables will be created to summarise the number of correct responses selected.

Confidence intervals will be generated around the percentage of participants that answer each knowledge question correctly for the overall and by-country results. The specific tables to be included will be finalised in the analysis plan.

No *a priori* thresholds of correct responses to the questions are established as targets for this study. Although there are no publicly reported accepted standards for such thresholds (Arias et al., 2016; EMA, 2017), sponsors and regulators often find reassurance if correct responses are reported by at least 80% of study participants.

Results from this study will be reviewed qualitatively to identify patterns suggesting the educational activities have been successful (e.g., consistently high percentages of correct responses across all questions), not successful (e.g., consistently low percentages of correct responses), or partially successful (e.g., high percentages for most responses and low for selected responses). Assessment of responses for each question can inform future educational materials. The results for each country will be evaluated and interpreted in the context of the local medical practices and the manner and timing of the RMM implementation.

The analysis will include a comparison of participants to what is known about the overall prescribing population, if data are available, to gauge how representative the final sample is.

Typically, questionnaire data are mostly complete, and each question will be analysed individually among those participants who respond. The analysis population will consist of respondents who were eligible for the study, who provided informed consent, and who completed at least one of the knowledge questions. The analysis plan will include an approach for handling missing data. No imputation of missing data will be performed.

All analyses will be performed using SAS 9.4 (or higher) statistical software (SAS, Cary, North Carolina). Programmes, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

The results will be compared qualitatively to the previous study and will focus on key concerns highlighted by previous survey.

9.9 Quality Control

This project will be conducted in accordance with the guidances described in Section 13 (Other Good Research Practices) and the internal standard operating procedures of participating institutions. The Office of Quality Assurance (OQA), an independent unit that reports to the vice president of , will oversee quality assurance for this study.

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, questionnaire, and study report, will undergo quality-control review, senior scientific review, and editorial review.

For the OQA will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board documentation. Such audits will be conducted by the OQA according to established criteria in standard operating procedures and other applicable procedures.

9.10 Limitations of the Research Methods

As with all cross-sectional surveys that depend on health care professionals agreeing to participate, some limitations are inherent. Many methodologic and operational challenges are well recognized (Arias et al., 2016). Although the study is designed to select a diverse and generally representative sample of physicians who have administered Ozurdex, there exists no exhaustive list of all physicians who have administered Ozurdex from which to draw a sample; hence, it is not possible to select a random sample of all physicians. Therefore, the study participants may not necessarily represent all physicians who have administered Ozurdex.

The study will include two sampling sources for recruitment: physician lists provided by Allergan and physician panels accessed via a vendor However, for

the former, per data privacy laws in Europe, Allergan can only share with [redacted] general lists of ophthalmologists (versus known prescribers of Ozurdex) with contact information that is publicly available (often limited to only a postal address). To provide [redacted] with more specific information, Allergan would first need to obtain consent from physicians to release their personal identifying information to a third party, a process not considered practical for this type of study.

In general, physician response rates for surveys have been somewhat low historically, and, given the limited information available on the physician lists, it is anticipated that recruitment from the lists will result in a low number of completed surveys.

In Germany, for post-authorization safety studies (PASS), the German Medicinal Products Act (§ 67 Abs. 6 AMG, § 63f AMG) requires that physician participation in the study, as well as any associated compensation, be reported to the Federal Association of Panel Doctors, the Central Federal Association of the Health Insurance Funds, and the German Association of Private Health Insurance Funds. To meet this reporting requirement, physicians must provide their name and lifelong physician identification number as part of the survey. As a result, it is anticipated that the potential pool of eligible responders and physician response to the survey may be particularly low in Germany.

Low response rates may result in higher likelihood that participating physicians are not representative of all prescribing physicians. Thus, the resulting estimates of physician understanding about Ozurdex may be biased. If participants discontinue the survey because they do not know how to answer the knowledge questions, then the frequency of substantial physician knowledge will be overestimated. Data will be collected to assess the number of physicians who begin but do not complete the questionnaire. This information can be used to help assess this potential bias. However, in our experience, almost all participants complete all items of the questionnaire.

In addition, as is true with most surveys, it is possible that participants who complete the questionnaire will differ from non-participants in characteristics measured in the questionnaire (e.g., knowledge of or reading the educational materials). The direction and magnitude of such potential participant bias is not known.

The study will target a total of 300 to 400 physicians (approximately 75 to 100 physicians per country). The majority of the analysis will focus on aggregated data across all countries. Although the report may display country-specific findings, there may be limitations with drawing country-specific conclusions.

Allergan sales representatives began distributing the revised educational materials in 2014, and distribution is ongoing. The survey will be conducted after physicians have received the revised Ozurdex educational materials and have had a chance to utilise that information in their practice, allowing for evaluation of how well they understand the safety information provided in the educational materials and apply it to their practices.

Pretesting of the questionnaire through formal cognitive pretesting with physicians in each country should facilitate accuracy of responses among physicians. The wording of the questions and response choices should be easily understood by physicians.

9.11 Other Aspects

None.

10 Protection of Human Subjects and Other Good Research Practice

This study will be conducted in accordance with all applicable ethical and regulatory requirements, including the 2008 version of the Declaration of Helsinki. The institutional review board at [redacted] (of which [redacted] is a division) will review the study protocol, questionnaires, and informed consent documents or grant an exemption from review. [redacted] will confirm the requirements for ethics committee review in each country and will obtain approvals in accordance with applicable national and local regulations (for any reviews that are determined necessary).

10.1 Informed Consent

Participant informed consent will be obtained for each physician who agrees to complete a questionnaire. Physicians will be asked to provide electronic acknowledgement of consent prior to completing the web-based questionnaire. Any identifying physician information required for the purposes of making payments and/or reporting payments will be collected and stored separately from questionnaire responses. Each participant will be tracked using a unique study identifying number.

10.2 Participant Confidentiality

Physicians will be given unique login information to complete the survey. The personal identifying information used or collected from physicians will be limited to that which is necessary for the purposes of recruitment, compensation, and to meet regulatory requirements for reporting payments made to physicians in each country, as applicable.

Any reports generated will not contain any participant identifiers. Only deidentified data will be made available to Allergan.

10.3 Compensation

Physicians will be paid nominal incentives to compensate them for their time in completing the survey. Physician payments will be made and reported according to local regulations in each country.

11 Management and Reporting of Adverse Events/Adverse Reactions

This study is not designed to collect information on individual AEs or adverse drug reactions, which are better collected using other study designs. AEs are not anticipated as part of the web-based physician survey because there will be no open-ended

questions. However, spontaneous AEs may be communicated by physicians during the qualitative cognitive pretesting interviews.

The cognitive pretest interviewers underwent safety training prior to the interviews. One AE was reported, and an AE report form was submitted to the Allergan Patient Safety Operations within 24 hours.

Any AE information received will be documented and reported following the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2014) and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004). The process for safety reporting will be further described in a safety reporting plan.

12 Plans for Disseminating and Communicating Study Results

The study protocol and final study report will be included in regulatory communications in line with the RMP, Periodic Safety Update Reports, and other regulatory reporting requirements. The study report will be prepared using a template following the GVP Module VIII Section B.6.3 (EMA, 2016) and will be posted in the EU PAS Register (ENCePP, 2016b).

In its Guidelines for Good Pharmacoepidemiology Practices, the International Society for Pharmacoepidemiology contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015); for example, results pertaining to the safety of a marketed medication. "…the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication."

If the results of the study are submitted to a conference or a journal, study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2016). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (von Elm et al., 2008).

Communication via appropriate scientific venues, e.g., International Society for Pharmacoepidemiology, will be considered.

The MAH and the investigator will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The MAH will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. The MAH and the research team are aware that the MAH should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within 2 weeks after first acceptance for publication (EMA, 2016).

13 Other Good Research Practice

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices* of the International Society for Pharmacoepidemiology (ISPE, 2015) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2017). The *European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study Protocols* (ENCePP, 2016a) has been completed (see Annex 2), and the study will be registered in the EU Post-Authorisation Studies Register (ENCePP, 2016b) before the study implementation commences.

The study is a PASS and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA, 2016), and with the 2012 EU pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII section VIII.B.6.3.1. “Progress reports” and VIII.B.6.3.2. “Final study Report” of the *Guideline on Good Pharmacovigilance Practices* (EMA, 2016).

The research team and study sponsor adhere to the general principles of transparency and independence in the ENCePP Code of Conduct (ENCePP, 2014).

14 References

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Evaluation of the Physician Education Component of the Ozurdex Risk Management Plan

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	See comment

Comments:

2.1.5 - The study is descriptive. There are no a priori hypotheses.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	0
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical data set is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.3 and 3.4 - The study is descriptive.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.1
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☐	☐	☒	9.2
4.2.5 Duration of follow-up?	☐	☐	☒	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	0

Comments:

This is a cross-sectional study with a one-time questionnaire to physicians

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation substudy)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

This is a study to evaluate physician's knowledge of safety and safe use of OZURDEX

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	0

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	0
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation substudy)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

This is a study to evaluate physician's knowledge of safety and safe use of OZURDEX

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.10
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.10
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	0

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	0
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	0
9.1.3 Covariates?	☒	☐	☐	0

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	0
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	0
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	0
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

This is a study to evaluate physician's knowledge of safety and safe use of OZURDEX.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.8
10.2 Are descriptive analyses included?	☒	☐	☐	9.8
10.3 Are stratified analyses included?	☒	☐	☐	9.8
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and antifraud protection, archiving)	☒	☐	☐	9.7.1
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation substudy, use of validation and external data, analytical methods)	☒	☐	☐	9.10
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1 and 9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	0

Comments:

Name of the main author of the protocol:

Annex 3.
Physician Questionnaire