Postauthorization Safety Study (PASS)

Acronym/title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	v2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Active substance	INN: Aflibercept; ATC code: S01LA05
Medicinal product	Eylea (aflibercept)
Product reference	EU/1/12/797/001 and EU/1/12/797/002
Procedure number	EMA/H/C/0002392
Study initiator and funder	Bayer AG
Research objective	To measure physician knowledge and understanding of the key information in the revised physician educational material for aflibercept
Country(-ies) of study	France, Germany, Italy, Spain and the United Kingdom
Author	PPD PPD

ATC = Anatomical Therapeutic Chemical (Classification System); EMA = European Medicines Agency; EU = European Union; INN = International Non-proprietary Names; PAS = postauthorization study.

Marketing authorization holder

Marketing authorization holder	Bayer AG
MAH contact person	PPD Bayer AG Muellerstrasse 178 13353 Berlin, Germany

MAH = marketing authorization holder.

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

List of tables

2. List of abbreviations

EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
INN	International Non-proprietary Name
MAH	marketing authorization holder
OS	observational study
PAS	postauthorization study
PASS	postauthorization safety study
RTI-HS	RTI Health Solutions
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor A

3. Responsible parties

Bayer AG is the marketing authorization holder of aflibercept (Eylea) in the European Union (EU) and the study initiator and funder of the study. Bayer is also responsible for fulfilling any obligations for reporting results to regulatory agencies. Bayer is collaborating with RTI Health Solutions (RTI-HS), an independent non-profit research organization. RTI-HS is responsible for the design, conduct, analysis, and reporting of the study. Kantar Health, a global research operations partner, is responsible for physician recruitment and data collection.

3.1 Study initiator and funder

Role:	OS Conduct Responsible
Name:	PPD
Role:	Qualified Person Responsible for Pharmacovigilance
Name:	PPD
Role:	MAH contact person (Regulatory Affairs)
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Data Manager
Name:	PPD
Role:	OS Epidemiologist
Name:	PPD
Role:	Regulatory Affairs responsible
Name:	PPD

MAH = marketing authorization holder; OS = observational study.

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborators/Committees

RTI Health Solutions 3040 Cornwallis Road, PO Box 12194 Research Triangle Park, NC 27709-2194, USA
PPD Co-Principal Investigator
PPD Co-Principal Investigator and PPD
PPD
PPD
PPD
PPD

Kantar Health GmbH Landsberger Str. 284, 80687 Munich, Germany
PPD

4. Abstract

Acronym/Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	v2.0 26 October 2018
Study type/study phase	PASS
Author	PPD PPD
Rationale and background	As part of the EU risk management plan for aflibercept, Bayer developed materials to educate both physicians and patients on the key safety information and safe use for aflibercept administered by intravitreal injection. Bayer, in collaboration with RTI-HS, completed prior physician and patient assessments in June 2017 (study number 16526; "wave 1 survey") to evaluate the effectiveness of the aflibercept educational materials and to gain a better understanding of physician and patient knowledge of the key safety information and safe use for aflibercept. Based on the results of that study and per a request from the EMA, Bayer is in the process of revising the Eylea Prescriber Guide. Bayer will distribute the revised aflibercept educational materials through April 2019. The current study includes a follow-up physician survey ("wave 2 survey") to evaluate the effectiveness of the risk minimization measures following revision and distribution of the educational materials.

Research objectives	The primary objective in this study is to measure physician knowledge and understanding of the key information in the revised educational material for aflibercept. Specifically, the following objectives will be addressed: • Investigate whether physicians received the revised educational materials • Assess physicians' knowledge and understanding of key safety information contained in the revised educational materials and assess how physicians use the materials in their daily practice
Study design	The study will be an observational, cross-sectional study of knowledge, understanding, and self-reported behavior among a sample of physicians with recent aflibercept experience in a total of up to 5 European countries. Physicians from a physician panel will be invited to complete a brief web-based questionnaire regarding their knowledge of key safety information in the aflibercept educational materials.
Population	Ophthalmologists will be eligible to participate if they have prescribed and/or administered aflibercept in the past 6 months. Countries included are France, Germany, Italy, Spain, and the United Kingdom.
Variables	The physician questionnaire will assess physician knowledge of the key safety messages outlined in the aflibercept educational material (prescriber guide and video) and evaluate their receipt and use of the aflibercept educational materials, as well as counseling of patients and distribution of the patient booklet.
Data sources	Data will be obtained through questionnaire responses.
Study size	The study will target 60 to 100 participating physicians per country, with a minimum of 300 physicians overall, to allow reasonable precision around estimates of participant knowledge and understanding of the revised educational materials.

Data analysis	Analyses will include a detailed review of responses to individual questions and potential summary measures across logical groupings of response items. Physician results will be stratified by country and other logical variables (e.g., practice setting, whether or not the physician received the educational materials). A detailed analysis plan describing methods of analysis and presentation, including table shells, will be developed before data collection is initiated. In addition to a description of the analysis of the questionnaire data, the analysis plan will include a comparison of characteristics of participants to the overall population of ophthalmologists, based on available data, to gauge how representative the final sample is.
Milestones	• Registration in the EU PAS register: before the start of data collection • Ethical review (as required): before the start of data collection • Distribution of revised educational materials: estimated through April 2019 • Start of data collection: approximately 3 to 5 months after distribution of educational materials is complete • Analytical data set completely available: approximately 7 to 10 months after start of data collection • Final study report available: latest Q1 2021 • Study progress will be reported annually with the periodic safety update reports throughout the study

EMA = European Medicines Agency; EU = European Union; PAS = postauthorization study; PASS = postauthorization safety study; Q1 = first quarter; RTI-HS = RTI Health Solutions.

5. Amendments

None

6. Milestones

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrollment do not require amendments to the protocol. Revised study timelines and milestones that do not constitute a need for a formal protocol amendment are kept as a stand-alone document (Table 3, Annex 1) that is available upon request.

Table 1. Milestones

Milestone	**Planned date**
Registration in the EU PAS register	Before the start of data collection
Ethical review (as required)	Before the start of data collection
Distribution of revised educational materials	Estimated through April 2019
Start of data collection	Approximately 3 to 5 months after distribution of educational materials is complete
Analytical data set completely available	Approximately 7 to 10 months after start of data collection
Final study report available	Latest Q1 2021
Study progress (reported with the periodic safety update reports)	Annually throughout the study

EMA = European Medicines Agency; EU = European Union; PAS = postauthorization study; Q1 = first quarter.

Note: The revised educational materials will be distributed independent of the study but are mentioned here for context. Data collection will start after the revised materials have been distributed and physicians have had sufficient time to receive and use them.

7. Rationale and background

Aflibercept is a compound administered as an intravitreal injection. Aflibercept is a fusion protein specifically designed to bind all forms of vascular endothelial growth factor A (VEGF-A) and placental growth factor, two proteins involved in the abnormal growth of new blood vessels (Eylea summary of product characteristics, 2018).

Aflibercept has been approved by the European Medicines Agency (EMA) in adults for the treatment of neovascular (wet) age-related macular degeneration, visual impairment due to macular edema secondary to central retinal vein occlusion, visual impairment due to macular edema secondary to branch retinal vein occlusion, visual impairment due to diabetic macular edema, and visual impairment due to myopic choroidal neovascularization.

Intravitreal injections, including anti-VEGF therapies, have been associated with some uncommon complications, such as endophthalmitis, transient increases in intraocular pressure, traumatic cataract, and retinal and vitreous detachment. Publications cite the range in frequency of complications associated with the use of intravitreal injections as less than 1% to 2%. Less serious and more common complications include conjunctival hemorrhage, vitreous floaters, and eye pain (Csaky and Do, 2009; Jeganathan and Verma, 2009).

As part of the European Union (EU) risk management plan for aflibercept, Bayer developed materials to educate both physicians and patients on the key safety information and safe use for aflibercept intravitreal use. The EU educational materials are intended to raise physicians' awareness and minimize the occurrence and consequences of the important identified risks of endophthalmitis, intraocular inflammation, transient intraocular pressure increase, epithelium tears, traumatic cataract, embryo and fetotoxicity, medication error, misuse, and off-label use.

Bayer in collaboration with RTI-HS completed physician and patient assessments in June 2017 (study number 16526; "wave 1 survey") to evaluate the effectiveness of the aflibercept educational materials and to gain a better understanding of physician and patient knowledge of the key safety information and safe use for aflibercept.

Based on the results of that study and a request from the EMA (procedure number EMEA/H/C/002392/II/0039), Bayer is in the process of revising the aflibercept prescriber guide with a focus on items that were of key concern in the previous survey (outlined in Section 8.1). Bayer will distribute the revised prescriber guide to physicians at least once through April 2019.

As described in this protocol, the current study includes a follow-up physician survey ("wave 2 survey") to evaluate the effectiveness of the risk minimization measures following revision and redistribution of the materials. Bayer has collaborated with RTI-HS to develop this observational postauthorization safety study (PASS) to assess physician knowledge and understanding of the key safety information in the educational materials developed by Bayer.

7.1 Overview of wave 1 survey results

The main results of the wave 1 survey (study16526) that led to the revision of the educational material and to conduct of this follow-up survey are summarized below. A total of 8,424 physicians were invited to participate. Of those who were invited, 798 completed the screener, 459 were eligible, 428 consented to participate, and 428 met the definition for a completed questionnaire.

In general, physicians' knowledge of questions related to aflibercept storage and preparation and injection procedures was high. However, more than a quarter of physicians (28%) incorrectly responded that they should dilate the eye before an aflibercept injection. In addition, in Spain, where it is common practice for hospitals to use one vial for multiple injections, nearly half of physicians (47%) reported that the aflibercept vial was reusable between patients.

Physician knowledge on dosing requirements was higher for wet age-related macular degeneration and lower for newer or less commonly prescribed indications. Some physicians responded that monitoring is required during the first 12 months for the treatment of wet age-related macular degeneration and the treatment of diabetic macular edema, even though there is no requirement for monitoring between injections during the first 12 months. Most physicians knew the recommended dose for aflibercept, and knowledge on questions related to excess volume of aflibercept varied. Overall, physicians' knowledge of actions to prepare patients for treatment with aflibercept was

high, and most physicians knew the contraindications for aflibercept use. Knowledge was also high for recognizing signs and symptoms of possible side effects. However, a quarter of physicians (25%) incorrectly responded that it is not necessary to evaluate a patient's vision immediately after an aflibercept injection. Twelve percent of physicians incorrectly responded that nothing needs to be done to manage the potential for increased ocular pressure.

Fifty-nine percent of physicians correctly reported that aflibercept should not be used in pregnancy unless the potential benefit outweighed the potential risk to the fetus, and an additional 27% of physicians took a more conservative approach and responded that aflibercept should never be used in pregnancy. Nearly half of physicians (48%) selected the correct time frame for which women of childbearing potential must use effective contraception. The lower levels of knowledge observed for this question may be due to the topic being less salient for the study population, given the patients' ages. However, since the wave 1 survey, aflibercept has been approved to treat additional indications in younger patient populations, so this topic remains important.

In general, physicians' knowledge was consistent across countries.

Most physicians reported that they received and reviewed the summary of product characteristics and the prescriber guide. Approximately half of physicians reported that they received the intravitreal injection procedure video and the patient booklet, and two-thirds of physicians who received the materials reviewed them. Likewise, half of physicians reported providing the patient booklet to most or all of their patients with variations across countries.

In response to the results of the wave 1 survey and subsequent feedback from the EMA on these results, the prescriber guide has been updated and modifications have been made to the questionnaire to align with revisions to the guide and EMA recommendations.

8. Research objectives

8.1 Primary objective

The primary objective in this study is to measure physician knowledge and understanding of the key information in the revised educational material, with particular focus on knowledge of concepts that were of key concern in the previous survey, including the following:

- The use of aflibercept in women of childbearing potential (with regard to contraception, pregnancy, and breastfeeding)
- The fact that dilation of the eye before an aflibercept injection is not necessary
- The need to evaluate vision immediately after an aflibercept injection
- The need to monitor patients following an aflibercept injection for elevation in intraocular pressure
- No reuse of the same vial or prefilled syringe because of risk of infection from this multiple use.

Specifically, the objective will be addressed in the following ways:

- By investigating whether physicians received the educational materials and distributed the patient booklet to their patients.

- By assessing physicians' knowledge and understanding of key safety information contained in the revised educational material and assess how physicians use the materials in their daily practice.

9. Research methods

9.1 Study design

The study will be an observational, cross-sectional survey of knowledge, understanding, and self-reported behavior among a sample of physicians with recent aflibercept experience in up to five European countries. A survey approach was selected for this study because the main information on knowledge and understanding of the educational material can be obtained only through direct interaction with physicians. Data collection will be initiated in each country at least 3 months after distribution of the revised educational materials is complete to allow time for prescribers to have received the revised prescriber guide and use the information in their practice.

Physicians (ophthalmologists) will primarily be recruited from a physician panel with the aim of obtaining a sample generally representative of physicians who have prescribed and/or administered aflibercept in the selected countries. The panel of physicians is owned and maintained by Lightspeed Health, a web-based survey research company and division of Kantar. Lightspeed Health recruits physicians from all specialties for various research purposes. The panel is composed of physicians derived from multiple sources (e.g., hospital books and directories, medical directories, physician referrals). Each panel member is recruited by telephone and opts in to the panel twice. A stringent sampling procedure for panel member recruitment is in place to target a representative demographic cross section. The panel was initially built years ago, using targets and quotas to recruit physicians with characteristics that would generally represent the entire population of physicians in a country. Since then, the panel management has conducted several campaigns to build and increase the membership of the panel so that its membership is similar to the population of the physicians in the country. A rigorous verification process is implemented to confirm potential panelists' practicing status. The verification process includes checking physician background data against the medical directories in the EU (General Medicine Council in the United Kingdom). Panel membership is only finalized once live contact and verification is made with the physician at an office location. Physicians on the panel are routinely asked to participate in surveys. Recruitment and maintenance of the panel members are independent of the study; therefore, we have no reason to believe that panel members are more or less likely to have received the Eylea educational materials.

Ophthalmologists on the panel currently represent approximately 15% to 20% of ophthalmologists practicing in each country. A comparison of data available for ophthalmologists on the panel and data available for the general population of ophthalmologists was attempted in each study country, including variables on practice setting, sex, and age to assess the representativeness of the panel. The results and limitations of this comparison are described in Section 9.2.4.

In order to increase the representativeness for a specific study, typically there is the option to set quotas for recruitment of physicians based on certain characteristics (e.g., age, gender, practice setting) so that the resulting participants will closely match the target population of interest on these characteristics, if feasible. However, due to the fact that the number of ophthalmologists on the panel is relatively limited, we intend to invite all ophthalmologists on the panel in each country to participate in order to reach the target sample size for the study (versus setting quotas for certain

characteristics). This approach is consistent with the wave 1 survey in which all ophthalmologists on the panel in France, Germany, Italy, Spain, and the United Kingdom were invited to participate.

If there are concerns about reaching the targeted sample size in a country, physician lists may be used to supplement recruitment. The physician lists comprise ophthalmologists who have prescribed or will potentially prescribe aflibercept. Because of data privacy requirements, information available on the lists will be limited to contact information that can be found in the public domain and obtained from internal Bayer sources unless existing consent/agreements are in place that allow Bayer to share more specific physician information. Therefore the "representativeness" of the list may not be evaluable.

An invitation will be sent via e-mail and/or regular mail and/or made by phone to each member of the selected sample of physicians, inviting them to participate and providing a link to a web-based questionnaire. Eligibility for the study will be determined at the start of the survey based on physicians' self-report. Following consent, physicians will be asked to complete the questionnaire evaluating their knowledge and understanding of key safety information, as well as their receipt and use of the aflibercept educational materials. It is anticipated that the wave 2 survey will include a mix of new participants and physicians who also participated in the wave 1 survey. The number of physicians who participated in both waves of the survey will be specified in the wave 2 final report.

Data from the questionnaire responses will be analyzed using descriptive tables to characterize the level of knowledge, understanding, and reported safe-use practices among these physicians, stratified by country and other relevant characteristics. The study design for the wave 2 survey closely aligns with the design of the wave 1 survey, and the results will be qualitatively compared across waves.

9.1.1 Primary endpoint(s)

This is a PASS survey study; no clinical endpoints will be assessed.

The questionnaire will collect information related to physician characteristics and experience with aflibercept, as well as assess physicians' knowledge and understanding of storage and preparation, proper injection technique, and the risks associated with intravitreal injection with aflibercept. In addition, the questionnaire will include items to investigate physician receipt and use of the revised educational materials for aflibercept.

The endpoints to be assessed are the percentage of physicians responding correctly to each individual knowledge question (e.g., the percentage of physicians who respond correctly that vials should not be used for multiple injections because of infection risk). The knowledge questions include items on storage and preparation of aflibercept, injection procedure, recommended dosing and patient monitoring, safe use precautions, and side effects. A more detailed list of variables is provided in Section 9.3.

9.2 Setting

This cross-sectional study will be conducted in the same five western European countries included in the original survey (the United Kingdom, Germany, France, Spain, and Italy) in order to compare results across survey waves. Five countries are included to provide some diversity in practice patterns and to observe physician knowledge in different settings. In addition, it is anticipated that

the drug utilization in these countries will be such that there will be a sufficient number of eligible physicians with aflibercept experience to participate in the study.

9.2.1 Eligibility

This study will be conducted with physicians (ophthalmologists) who prescribe and/or administer aflibercept in the target countries.

9.2.2 Eligibility criteria

- Has signed informed consent
- Is a licensed and practicing ophthalmologist
- Has prescribed and/or administered aflibercept to at least one patient in the past 6 months

9.2.3 Withdrawal

Each physician may discontinue participation at any time during the survey without giving a reason. If a physician wants to stop participating in the study, no further data will be collected.

9.2.4 Representativeness

No comprehensive lists of all ophthalmologists performing intravitreal injections per country could be identified after an exploration into available data sources. Therefore, the physician sampling frame will be constructed primarily from a physician panel and, if necessary, supplemented with physician lists provided by Bayer. Details of the physician panel are outlined in Section 9.1. The information available on physicians from these sample sources is limited as is the information available for the population of ophthalmologists in general. However, in three of the five countries, we were able to compare the available characteristics of the physicians on the panel[1] with summary data that were publicly available on the general population of ophthalmologists. This comparison included age, sex, and practice setting variables in France, and age and sex variables in Germany and the United Kingdom. We were not able to identify characteristics of the general population of ophthalmologists in Italy or Spain.

In France, comparing the data from the panel to the general population of ophthalmologists showed a similar proportion of physicians worked in an office setting (> 64% in both countries), the panel had a slightly higher proportion of males than females (66% vs. 56%, respectively), and the panel was slightly older (78% vs. 68% who were 50 years or older) (Ministère des Solidarités et de la Santé, 2014). In Germany, the panel and the general population of ophthalmologists had a similar proportion that worked in an office setting (83% vs. 82%), but the panel had a somewhat higher proportion of males than females (69% vs. 52%) (Bundesaerztekammer, 2017). In the United Kingdom, the panel had the same proportion of males as the general population of ophthalmologists (74%), but the panel was slightly younger (65% vs. 57% were 49 years or younger) (Royal College of Ophthalmologists, 2016).

[1] The panel requests profile data including sex, age range, and practice setting (i.e., hospital or office) from physicians who enroll as a panelist. However, provision of this information by physicians is voluntary and is therefore incomplete for some ophthalmologists on the panel, and for data that is provided, it is the responsibility of the physician to update the data as needed.

The results of the limited comparison described above do not provide strong concerns about the representativeness of the participating ophthalmologists in the panel in the three countries.

Given that ophthalmologists qualified and equipped to do intravitreal injections are probably a fairly homogeneous subset of ophthalmologists in terms of education and practice setting, the potential for selection bias based on education, experience, and practice setting in this survey is expected to be limited. As is true with all voluntary surveys, it is possible that survey respondents may differ from the target population in characteristics that may be related to knowledge or behaviors being measured in the study.

9.2.5 Visits

This is a one-time cross-sectional survey of physicians, conducted electronically; there are no in-person visits.

9.3 Variables

The physician questionnaire will be based on the revised educational materials (prescriber guide and video) available at the time the questionnaire is developed. It will contain closed-ended questions (e.g., multiple choice, true/false), with no free-text response fields, eliciting responses measuring physician knowledge and understanding of the key information in the educational material for aflibercept. The physician questionnaire will include items in the following content areas:

- Storage and preparation of aflibercept
- Aflibercept dosing information
- Preparing the patient for treatment with aflibercept
- Aflibercept contraindications
- The use of aflibercept in women of childbearing potential (with regard to contraception, pregnancy, and breastfeeding)
- Sterile techniques to minimize risk of infection, including periocular and ocular disinfection
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- The restriction against reusing the same vial or prefilled syringe because of risk of infection
- The fact that dilation of the eye before an aflibercept injection is not necessary
- The need to evaluate vision immediately after an aflibercept injection
- The need to monitor patients following an aflibercept injection for elevation in intraocular pressure
- Key signs and symptoms of intravitreal injection-related adverse events (i.e., endophthalmitis, cataract, transient intraocular pressure increase, vitreous detachment, and conjunctival and retinal hemorrhage) and medication error/overdose

The questionnaire will also include the following items to investigate physician receipt and use of the prescriber educational materials:

- Receipt and review of the summary of product characteristics, prescriber guide, intravitreal injection procedure video, and indication-specific patient booklet, as well as questions to gauge the helpfulness of these materials
- Estimated time between the physicians' review of the prescriber guide and completion of the survey
- An estimate of the number of patients to whom physicians provide the patient booklet, timing of this distribution, and reasons for not providing the booklet

In addition, the physician questionnaire will include queries on the following items to characterize the physicians and their practices:

- Physicians' focus within ophthalmology
- Physicians' practice setting
- Average number of anti-VEGF intravitreal injections the physician administers each month
- Average number of aflibercept injections the physician administers each month
- Timing of last aflibercept injection
- Years in practice
- Gender
- Age

The questionnaire is anticipated to take 20 to 25 minutes to complete.

9.4 Data sources

The source of information for the study will be self-reported data collected from physicians using standard questionnaires with closed-ended response choices.

The physician questionnaire has been drafted using best practices for instrument development. The questions have been tailored to the study aims and the information provided in the educational material. Other questions will obtain information needed to assess potential differences across subgroups and identify biases (e.g., demographics, experience prescribing and administering aflibercept).

To thoroughly evaluate the physician questionnaire in preparation for fielding the original (wave 1 survey) study, the questionnaire was tested through cognitive interviews with physicians in each country. The questionnaire was tested in local languages to ensure that the introductory material, consent form, and questionnaire items (question stems and response choices) were culturally appropriate and easily and correctly understood by individuals similar to those who would participate in the full survey.

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 questionnaires 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 questionnaires.

Cognitive pretesting of the physician questionnaire was conducted with 25 physicians across the five study countries who prescribed and/or administered aflibercept for (wet) age-related macular degeneration or central retinal vein occlusion. To the extent possible, physicians who participated in the cognitive interviews will be excluded from participating in the study.

9.5 Study size

The study will target 60 to 100 participating physicians per country, for a minimum of 300 physicians overall, to allow reasonable precision around estimates of physicians' knowledge and understanding of the prescriber guide. Because of the limited number of eligible physicians on the panel or list, it is anticipated that the wave 2 survey will include a mix of new participants and physicians who participated in the wave 1 survey. If we assume that the total sample of participating physicians can be treated as a simple random sample and that the percentage of correct responses to a true/false question is 85%, then for a minimum sample size of 300, the two-sided 95% confidence interval will be 80.4% to 88.8%. Table 2 shows the exact 95% confidence limits assuming various combinations of sample size and correct response percentages.

Table 2. Exact 95% confidence limits for various combinations of physician sample size and correct response percentage

Physician Sample Size	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	80	70.8	87.3
100	85	76.5	91.4
300	80	75.0	84.4
300	85	80.4	88.8
500	80	76.2	83.4
500	85	81.6	88.0

9.6 Data collection and management

9.6.1 Data collection

A web-based electronic data capture (EDC) system will be used in this study. The panel provider will send an invitation via e-mail and/or regular mail and/or made by phone to the selected sample of 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 3 times if they have not already responded. Each invited physician will be asked to log in to the

study website by entering a unique identification number and password assigned to each participant and provided in the invitation to participate. The questionnaire will begin with informed consent. After participants 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 aflibercept at least once within the past 6 months.

The questionnaire will be self-administered (closed-ended questions with predefined answers) and can be completed at the participants' convenience. Although participants 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, pick up where they left off, should that be necessary. Participants will not be able to go back and change answers to previous questions. This restriction minimizes the likelihood of the respondent searching for answers via the web or other sources or being influenced by answers to subsequent questions. Participants will also not be allowed to regain access to the questionnaire once it has been completed. Based on potential country-specific requirements, the recruitment process and questionnaire may be different between countries. Country-specific differences will be described and appended to the final study protocol.

9.6.2 Data management

RTI-HS will develop a data management plan 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. Because of the self-reported nature of the data, no changes will be made to data that appear to be incorrect or inconsistent during data cleaning.

The panel provider will develop the web-based EDC system. RTI-HS 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 authorizing 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 a review of interim analysis files for consistency, programming edit checks in preparation for statistical analysis, and merging data sets, if required.

9.7 Data analysis

A detailed analysis plan describing methods of analysis and a presentation that includes table shells will be developed before the start of data collection. Version 1.0 of the statistical analysis plan is provided as a stand-alone document referenced in Annex 1, Table 3, of this protocol. The statistical analysis plan will be finalized before study database lock.

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. Analysis tables will include the frequency and percentage of physicians who select each response to each individual question.

As outlined in Section 9.1.1, the endpoints to be assessed are the percentage of physicians responding correctly to each individual knowledge question. In addition, for knowledge questions with multiple correct responses, derived variables will be created to summarize 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 finalized in the analysis plan.

Results from this study will be reviewed qualitatively to identify patterns suggesting that 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 percentages for selected responses). The results for each country will be evaluated and interpreted in the context of the local medical practices and the method and timing of the risk minimization measures implementation.

Any available data on the general population that are identified will be used to compare characteristics of participants with available data on the overall population of ophthalmologists. Survey results will be stratified on the related variables (e.g., age, gender, practice setting) to see whether an imbalance of the characteristic could cause a bias in the overall study results. An imbalance would lead to a bias in the knowledge results only if there were differences in knowledge between the different levels of the imbalanced characteristic. For example, if the study sample includes a significantly higher percentage of males than that of the overall population of ophthalmologists, an examination of knowledge by gender will identify whether this imbalance would cause a bias in the overall results. If the stratified results show that knowledge is similar by gender, the imbalance would not bias the overall results.

In addition to the stratification performed to assess responder bias, the overall results tables of the knowledge questions will be stratified by other variables (e.g., number of years treating patients, physicians' focus within ophthalmology, time between when the physicians reviewed the prescriber guide and took the survey, average number of aflibercept injections the physician administers each month) to identify whether any of these variables have an impact on knowledge.

Typically, questionnaire data are mostly complete, and each question will be analyzed individually among those participants who respond. The analysis population will consist of respondents who were eligible for the study, provided informed consent, and completed at least one of the knowledge questions. The analysis plan will include an approach for handling missing data.

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

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

9.7.1 Statistical considerations

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.

9.8 Quality control

This project will be conducted in accordance with the guidance described in Section 10.2 (Regulatory authority approvals/authorizations) and the internal standard operating procedures of participating institutions. The RTI-HS Office of Quality Assurance, an independent unit that reports to the vice president of RTI-HS, will oversee quality assurance for this study.

Standard operating procedures will be used to guide 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 RTI-HS, the Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry, data transfer procedures and documentation, and institutional review board documentation. Such audits will be conducted by the Office of Quality Assurance, according to established criteria in standard operating procedures and other applicable procedures.

9.8.1 Storage of records and archiving

All data for the physician survey will be electronic. Bayer will ensure that all relevant data for this study will be stored after the end or discontinuation of the study for at least 15 years. Any data and programs from statistical programming performed to generate results will be stored within the programming system for at least 15 years.

9.9 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, 2016). Although the study is designed to select a diverse and generally representative sample of physicians who have recent experience with aflibercept, there is no exhaustive list of all physicians who have prescribed or administered aflibercept 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 prescribed/administered aflibercept.

The primary source of physician recruitment will be the physician panel. Physician lists will also be used to supplement recruitment if needed to meet the target sample size in each country. Per data privacy laws in Europe, Bayer can only share with RTI-HS general lists of ophthalmologists (vs. known prescribers of aflibercept) with contact information that is publicly available (often limited to

a postal address). To provide RTI-HS with more specific information, Bayer 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. In Germany, for postauthorization safety studies, 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 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 aflibercept may be biased. If participants discontinue the survey because they do not know how to answer the knowledge questions, 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.

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.

In addition, the sample does not account for individuals who could not participate because of the mode of data collection (i.e., Internet access). However, it is anticipated that the majority of physicians will have Internet access.

A comparison of participants and non-participants in the physician assessment will not be possible because physicians who do not wish to participate in the survey are likely not to respond to the invitation. However, if data are available, we will compare characteristics of the participants to what is known about the overall ophthalmologist population. Some potentially important characteristics, such as physician skill, annual volume of injections, years in practice, will be available only from the study participants and cannot be compared with non-participants or the total ophthalmologist population. Ophthalmologists administering intravitreal injections are a highly trained and experienced subset of all ophthalmologists, and we would expect considerable homogeneity between participants and non-participants.

The study will target a minimum of 300 physicians (approximately 60 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.

Bayer anticipates initial distribution of the revised educational materials through April 2019. The survey will be conducted after physicians have received the revised Eylea Prescriber Guide and have had a chance to use the information in their practice, which allows for evaluation of how well they understand the safety information provided in the educational materials and apply it to their practices.

9.10 Other aspects

Not applicable

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study to evaluate physicians' knowledge and understanding of key safety information, as well as their receipt and use of the educational materials for aflibercept. There is no patient involvement in the study.

10.2 Regulatory authority approvals/authorizations

The study will be carried out with guidelines and regulations of EMA and applicable local law(s) and regulation(s) (e.g., Regulation (EU) No 520/2012 [European Commission, 2012]). Recommendations given by other organizations also will be followed (e.g., European Federation of Pharmaceutical Industries and Associations, 2007; European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP, 2017]). The International Conference of Harmonisation-Good Clinical Practice guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP module VI, rev1 [EMA, 2014], and because the study qualifies as a PASS, GVP module VIII, rev3[EMA, 2017]) will be followed.

10.3 Independent ethics committee or institutional review board

The institutional review board at RTI International (of which RTI-HS is a division) will review the study protocol, questionnaire, and informed consent document or grant an exemption from review.

The requirements for ethics committee review will be confirmed in each country and approvals will be obtained in accordance with applicable national and local regulations (for any reviews that are determined necessary).

10.4 Physician information and consent

Physicians who are interested in participating in the study will be required to provide electronic acknowledgment of informed consent before completing the web-based questionnaire.

10.5 Patient insurance

Not applicable.

10.6 Confidentiality

Bayer and all investigators will ensure adherence to applicable data privacy protection regulation.

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

Only deidentified data will be made available to Bayer. Thus, any reports generated will not contain any participant identifiers. Data will be provided to Bayer in aggregate only and will not be linked to individual physicians.

10.7 Compensation

Participating physicians will be paid nominal incentives to compensate them for their time in completing the study questionnaire.

11. Management and reporting of adverse events/adverse reactions

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

12. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov" and in the EU PAS register at "http://www.encepp.eu/encepp_studies/indexRegister.shtml." Results will be disclosed in a publicly available database within the standard timelines.

If a competent authority or EMA requests progress reports, these will be provided in agreed frequency and content.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses. The marketing authorization holder (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 to provide comments before 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 authorized the final manuscript of the article within 2 weeks after first acceptance for publication (EMA, 2016). Current guidelines and recommendations on good publication practice will be followed (e.g., Good Clinical Practice [GPP]2 Guidelines [Graf, 2009]; Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] von Elm, 2008).

13. References

Arias A, DiSantostefano R, Gilsenan A, Madison T, Matus D, Primatesta P, et al. Evaluating the effectiveness of additional risk minimisation measures via surveys in Europe: challenges and recommendations. 2016. Available at: https://pharmacoepi.org/pub/f46953df-de69-31e7-8f74-725bd7fa685f Accessed 16 October 2018.

Bundesaerztekammer [German Medical Association]. Bundesgebiet gesamt [in German]. December 2017. Available at: http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/Statistik2017/Stat17AbbTab.pdf. Accessed 16 October 2018.

Csaky K, Do DV. Safety implications of vascular endothelial growth factor blockade for subjects receiving intravitreal anti-vascular endothelial growth factor therapies. Am J Ophthalmol. 2009;148(5):647-56.

European Commission. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. 2012. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed 16 October 2018.

European Federation of Pharmaceutical Industries and Associations. Code on the promotion of prescription-only medicines to and interactions with healthcare professionals. Oct 2007.

European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (EMA /204715/2012 Rev 2). 28 March 2017 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf. Accessed 16 October 2018.

European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1). 8 September 2014. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-vi-management-reporting-adverse-reactions_en-0.pdf Accessed 16 October 2018.

European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3 Corr). 09 October 2017. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf Accessed 16 October 2018.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (EMA/95098/2010 Rev.7). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; July 2018. Available at: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideonMethStandardsinPE_Rev7. Accessed 16 October 2018.

Eylea summary of product characteristics. Electronic Medicines Compendium. 30 July 2018. Available at: https://www.medicines.org.uk/emc/medicine/27224. Accessed 16 October 2018.

Graf C, Battisti WP, Bridges D, Bruce-Winkler V, Conaty JM, Ellison JM, et al. International Society for Medical Publication Professionals. Research methods and reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. BMJ. 2009 Nov 27;339:b4330.

Groves R, Fowler F, Couper M, Lepkowski J, Singer E, Tourangeau R. Survey methodology. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2009.

Jeganathan VS, Verma N. Safety and efficacy of intravitreal anti-VEGF injections for age-related macular degeneration. Curr Opin Ophthalmol. 2009 May;20(3):223-5.

Ministère des Solidarités et de la Santé [Ministry of Solidarities and Health]. La démographie des médecins (RPPS): Professions de santé et du social| 2014. [in French]. 2014. Available at: http://drees.solidarites-sante.gouv.fr/etudes-et-statistiques/open-data/professions-de-sante-et-du-social/la-demographie-des-professionnels-de-sante/la-demographie-des-medecins-rpps/article/la-demographie-des-medecins-rpps. Accessed 20 April 2018.

The Royal College of Ophthalmologists. Workforce census 2016. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2017/03/RCOphth-Workforce-Census-2016.pdf. Accessed 20 April 2018.

von Elm E, Altman D, Egger M, Pocock SJ, Gøtzsche PC, and Vandenbroucke JP. STROBE-Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2008 Apr; 61(4):344-9.

Annex 1: List of stand-alone documents

Table 3. List of stand-alone documents

Document name	Final version and date (if available)*
Physician Questionnaire	V 2.0, <draft> 26 October 2018
Eylea Prescriber Guide	12 June 2018
Statistical Analysis Plan	V 1.0, <draft> 22 October 2018

Notes: Draft versions are indicated by <draft> in brackets and date.

Annex 2: ENCePP checklist for postauthorization safety study (PASS) protocols

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 Physician Knowledge of Safety and Safe Use Information for Aflibercept in Europe: A Follow-up Physician Survey

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[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
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:	☒	☐	☐	7
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)	☒	☐	☐	8
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 This 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
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	

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

[3] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
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)	☐	☐	☒	
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:

3.4 and 3.5- Study is descriptive

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.6
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	9.1.1
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1/9.2.2

Comments:

This is a cross sectional study with a one-time questionnaire with 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 sub-study)	☐	☐	☒	
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 Eylea

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?	☒	☐	☐	8.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.0
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 sub-study)	☐	☐	☒	
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 Eylea

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)	☒	☐	☐	9.2.4
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.2.4
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

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, subgroup 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)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	
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)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
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 Eylea

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
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 anti-fraud protection, archiving)	☒	☐	☐	9.6.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
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

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?	☐	☐	☒	

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: 26/October/2018

Signature: _____

Annex 3: Additional information

Not applicable

Annex 4: Description of amendments

None

Annex 5: Signature pages

Signature Page - Co-Principal Investigator

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 5Mar2019, PPD

Signature Page - Co-Principal Investigator

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 7 Mar 2019 , PPD

Signature Page – OS Conduct Responsible and OS Epidemiologist

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Bayer AG

Date, Signature: 22.3.19, PPD

Signature Page – Qualified Person Responsible for Pharmacovigilance

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Bayer AG

Date, Signature: 7-3-2019, PPD

Signature Page – MAH Contact Person (Regulatory Affairs)

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Bayer AG

Date, Signature: 20 March 2019, PPD

Signature Page – OS Safety Lead

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Bayer AG

Date, Signature: 06-MAR-2019, PPD

Signature Page – OS Medical Expert

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Bayer AG

Date, Signature: 5.3.19 , PPD

Signature Page – OS Statistician

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

RTI Health Solutions

Date, Signature: 5 MAR 2019, PPD

Signature Page – OS Data Manager

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

RTI Health Solutions

Date, Signature: 5 Mar 2019, PPD

Signature Page – Regulatory Affairs Responsible

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Protocol version and date	Version 2.0, 26 October 2018
IMPACT study number	20285
Study type/study phase	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not yet registered
Medicinal product / Active substance	Eylea (aflibercept) / INN: Aflibercept; ATC code: S01LA05
Study initiator and funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Bayer AG

Date, Signature: 5 March 19, PPD