Post-Authorization Safety Study (PASS) Report - Study Information

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
Report version and date	V1.0, 21 AUG 2020
Study type/study phase	☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS30727
Active substance	INN: Aflibercept; ATC code: S01LA05
Medicinal product/medical device/combination 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 question and objectives	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

Marketing authorization holder

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

Confidentiality statement:

Table of contents

List of tables

List of figures

1. 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
Report version and date **Author**	V1.0, 21 AUG 2020 PPD
Keywords	Eylea (aflibercept); post-authorization safety study; evaluation of risk-minimization measures; physician survey
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 PPD 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 per a request from the European Medicines Agency (EMA), Bayer revised the prescriber guide and distributed the revised aflibercept educational materials through May 2019. The current study included 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 question and objectives	The primary objective in this study was to assess physician knowledge and understanding of the key information in the revised educational materials for aflibercept. Specifically, the following objectives were to 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 was an observational, cross-sectional study of knowledge, understanding, and self-reported behavior among a sample of physicians with recent aflibercept experience in 5 European countries. Physicians from an online panel were invited to complete a web-based questionnaire regarding their knowledge of key safety information in the aflibercept educational materials.
Setting	The study was conducted in France, Germany, Italy, Spain, and the United Kingdom
Subjects and study size, including dropouts	Physicians were eligible to participate if they had prescribed and/or administered aflibercept to at least one patient in the past 6 months. A total of 4,715 physicians were invited to participate in wave 2; 878 physicians responded. Of the physicians who responded, 504 were eligible, 52 did not complete the screening questions, and 322 were ineligible because they had not prescribed aflibercept nor administered an aflibercept injection in the past 6 months. Of the 504 eligible, 28 did not consent to participate and 22 did not meet the definition for a completed questionnaire (i.e., did not answer at least one knowledge question). The remaining 454 physicians completed the wave 2 questionnaire and are included in this analysis. The overall response rate was 9.6%.
Variables and data sources	The source of information for the study was self-reported data collected from physicians using a standard questionnaire with closed-ended response choices. The questionnaire assessed physician knowledge of the key safety messages outlined in the aflibercept educational material and evaluated physicians' receipt and use of the educational materials, as well as counseling of patients and distribution of the patient booklet.
Results	Questionnaire responses from the 454 wave 2 participants were analyzed using descriptive tables to characterize the level of knowledge, understanding, and reported safe-use practices among these physicians. Knowledge ranged from 83% to 92% for identifying 4 true statements, including the statement "use of more than one injection from the vial can lead to contamination and subsequent infection" which was correctly identified as true by 84% of physicians. The proportion of correct responses for identifying 3 false statements on this topic ranged from 44% to 83%; this included the statement "the vial of Eylea is reusable between patients and can be used for multiple injections," which was correctly identified as false by 83% of physicians.

	Physicians' knowledge for recognizing the recommended dose of aflibercept was 78% and the fact that the vial contains more volume than the recommended dose was 82%. Knowledge was lower for specifics around removing the drug from the vial (58%). Overall, physicians' knowledge of actions to prepare patients for safe use of aflibercept ranged from 67% to 94% on 3 individual items. Knowledge of contraindications ranged from 82% to 92% on 3 individual contraindications. Most physicians (80%) either correctly indicated that aflibercept should not be used in pregnancy unless the potential benefit outweighed the potential risk to the fetus or seemed to favor a more conservative approach and indicated that aflibercept should never be used in pregnancy. Slightly more than half of physicians (53%) selected the correct time frame for which women of childbearing potential must use effective contraception, and the majority (76%) correctly indicated that aflibercept is not recommended for women who are breastfeeding. Regarding injection procedures, knowledge for appropriate use of topical anesthesia was 89% and knowledge for appropriate use of disinfectant was 92%. When asked to identify steps that should be taken prior to marking the scleral injection site, most physicians correctly selected "cover the eye with a sterile drape" (84%) and/or "insert a sterile lid speculum" (76%). Less than one-fourth (22%) of physicians indicated that the pupil should be dilated (this was not a correct response option). Of these physicians, 58% indicated that pupil dilation is performed for regular assessment of the underlying disease or other assessments, and 54% indicated it is done based on requirements/recommendations by national or local guidelines for intravitreal injections, local protocols, or other recommendations. Slightly more than half of physicians (54%) correctly reported that patients' vision should be evaluated immediately after an injection, by hand movements or counting fingers. Most physicians (83%) knew that an increase in intraocular pressure has been seen within 60 minutes after an injection. Knowledge was lower for identifying each of the following actions to take in relation to potential increased intraocular pressure: ensuring that sterile equipment is available to perform paracentesis if necessary (56%) and monitoring patients after the injection procedure (e.g., tonometry or check for perfusion of the optic nerve head) (62%). Knowledge for the need to instruct patients to report without delay, any symptoms suggestive of intraocular inflammation was 81% and was 87% for endophthalmitis. Knowledge for

	recognizing signs, symptoms, or diagnoses of possible side effects ranged from 69% to 92% for 4 individual side effects. Most physicians reported that they received the SmPC (89%) and prescriber guide (82%). More than half of physicians (54%) reported that they received the intravitreal injection procedure video, and two-thirds (65%) reported that they received the indication-specific patient booklet, including a patient booklet audio CD and the patient information leaflet.
Discussion	The study successfully evaluated whether physicians receive the educational materials for aflibercept and assessed physician knowledge and understanding of key safety information, as well as the use of the materials. Physicians reported receipt of the SmPC and prescriber guide was high (at 89% and 82%, respectively). The relatively high level of knowledge among physicians also suggests that the key safety information is available to the treating physicians. Physicians' knowledge of most important topics was generally high. For example, knowledge on possible side effects ranged from 69% to 92%. In general, the observed patterns of knowledge among the physicians are as expected—with greatest knowledge on the most important risks emphasized in the educational materials and SmPC and lower knowledge on topics that are less frequently encountered and for which we would assume that physicians would consult the label and/or prescriber guide for information rather than relying on their memory (e.g., use in women of childbearing potential).
Marketing authorization holder(s)	Bayer AG
Names and affiliations of principal investigators	PPD

EMA = European Medicines Agency; EU = European Union; PPD SmPC = Summary of Product Characteristics.

2. List of abbreviations

DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
INN	International Nonproprietary Name
MAH	Marketing Authorization Holder
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PPD	PPD
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor A

3. Investigators

Principal Investigators	Country	Institutional Affiliation
PPD	United States	PPD
	United States	
	United States	

4. Other 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 collaborated with PPD PPD an independent nonprofit research organization. PPD was responsible for the design, conduct, analysis, and reporting of the study. Kantar, a global research operations partner, was responsible for physician recruitment and data collection.

4.1 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.

4.2 Collaborators/Committees

PPD USA
PPD Co-Principal Investigator
PPD Co-Principal Investigator PPD
PPD
PPD
PPD
PPD
PPD

PPD
PPD

5. Milestones

Milestone	Planned date	Actual date	Comments
EMA approval of wave 2 protocol		28 FEB 2019	
Distribution of revised educational materials	Estimated through APR 2019	MAY 2019	
Registration in the EU PAS register	Before the start of data collection	04 SEP 2019	
Approval of exemption from IRB review	Before the start of data collection	13 SEP 2019	

Milestone	Planned date	Actual date	Comments
Start of data collection	Approximately 3-5 months after distribution of educational materials is complete	8 OCT 2019	
End of data collection		15 APR 2020	
Analytical data set completely available	Approximately 7-10 months after start of data collection	23 April 2020	
Final report of study results	Latest Q1 2021	October 2020	
Study progress (reported with the periodic safety update reports)	Annually throughout the study	Submitted in JAN 2020 with PSUR No. 9	

EMA = European Medicines Agency; EU = European Union; IRB = institutional review board; PAS = post-authorization study; Q1 = first quarter.

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

6. Rationale and background

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 (1).

Intravitreal aflibercept (Eylea®) has been approved by the European Commission (EC) 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. For treatment of exudative retinal diseases, aflibercept is administered through intravitreal injection.

Intravitreal injections, including anti-vascular endothelial growth factor (VEGF) therapies, have been associated with complications, such as endophthalmitis, intraocular inflammation, 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 (2,3).

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 intravitreal aflibercept 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 PPD 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 European Medicines Agency (EMA) (procedure number EMEA/H/C/002392/II/0039), Bayer revised the aflibercept prescriber guide with a focus on items that were of key concern in the previous survey (outlined in Section 7). The EMA agreed version of the prescriber guide is provided as a stand-alone document referenced in Annex 1, Table 1-1 of this report. Upon member-state health authority approval of the updated educational material and the distribution plan, Bayer distributed the revised prescriber guide to physicians through May 2019.

The current study included 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 collaborated with PPD to develop this observational post-authorization safety study to assess physician knowledge and understanding of the key safety information in the educational materials developed by Bayer. The study protocol was approved by the EMA in February 2019. This report summarizes results from the wave 2 physician assessment.

7. Research question and objectives

The primary objective in this study was 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 pupil 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 because of risk of infection from multiple use

Specifically, the following objectives were to 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 assessing how physicians use the materials in their daily practice

As part of good research practices, the protocol, and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist were registered in the EU Post-Authorization Study Register (4) before the start of wave 2 data collection. The study was designed and implemented in line with the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices* (5); the EMA *Guidelines on Good Pharmacovigilance Practices, Module VIII – Post-authorization Safety Studies* (6); and the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (7). The contract between PPD and Bayer includes independent publication rights.

The study received exemption from review by the PPD for wave 2 data collection on 13 SEP 2019.

8. Amendments and updates

None.

9. Research methods

9.1 Study design

The wave 2 study was an observational, cross-sectional survey of knowledge, understanding, and self-reported behavior among a sample of physicians with recent aflibercept experience in five European countries. A cross-sectional 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 started in each country at least 3 months after the initial distribution of the revised educational materials to allow time for prescribers to have received the revised prescriber guide and use the information in their practice.

Physicians (ophthalmologists) were recruited from a physician panel[1] with the aim of obtaining a sample generally representative of physicians who have prescribed and/or administered aflibercept in the selected countries. Because the number of ophthalmologists on the panel is relatively limited, we invited all ophthalmologists on the panel in each country to participate in order to reach the target study size.

Physicians were invited to participate via an e-mail, which included a link to the web-based questionnaire. Interested physicians logged in to the study website by entering a unique identification number and password. The physicians then completed informed consent and a screening question to confirm that they had prescribed and/or administered aflibercept to at least one patient within the past 6 months. Physicians who completed the consent and were deemed eligible could continue and complete the self-administered questionnaire. Physicians were not able to go back to previous questions, which kept them from changing their answers based on subsequent questions.

Reminders were used in all countries to boost response. Additional efforts were made in Germany in an effort to reach the target study size, including extending the data collection period, sending additional reminders, use of two additional partner panels, and following up by phone with physicians who had started the survey but had not completed it.

The web-based format for completion of the consent form and self-administered questionnaire was chosen because of the efficiency and utility of the mode (e.g., question-branching logic and ability to stop respondents from going back to previous questions to change answers).

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[1] 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. 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. More details on the panel are provided in the study protocol.

Most physicians have convenient access to complete a web-based questionnaire, so the use of this technology is not believed to have introduced a respondent bias.

Data collection ran from 08 OCT 2019 to 15 APR 2020.

The wave 2 survey included 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 is specified in Section 10.1.

Questionnaire responses were 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 aligned with the design of the wave 1 survey. A number of questions were added or modified in the wave 2 survey as outlined in Section 9.4. The results have been qualitatively compared across waves. A graphical view of the comparison is included in Annex 5, and a summary of differences is provided in Section 10.5.

A comparison of participants to 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 participants. The results and limitations of this comparison are described in Section 10.5.4.

9.2 Setting

This cross-sectional study was conducted in the same five western European countries included in wave 1 (the United Kingdom [UK], Germany, France, Spain, and Italy) in order to compare results across survey waves. Five countries were included to provide some diversity in practice patterns and to observe physician knowledge in different settings. In addition, it was anticipated that drug use in these countries would be such that there would be a sufficient number of eligible physicians with aflibercept experience to participate in the study.

9.3 Subjects

9.3.1 Eligibility

This study was conducted with physicians (ophthalmologists) who prescribed and/or had administered aflibercept in the target countries.

To be eligible for the study, physicians met all of the following eligibility criteria:

- Provided informed consent
- Were a licensed and practicing ophthalmologist
- Prescribed and/or administered aflibercept to at least one patient in the past 6 months

9.4 Variables

The physician questionnaire was based on the revised prescriber guide available at the time the questionnaire was developed. It consisted of closed-ended questions (e.g., multiple choice, true/false), with no free-text response fields and included items in the content areas below. The questionnaire was largely the same as wave 1 except for a few questions that were added or modified to further address concepts that were of key concern in the previous survey. Questions related to the following concepts were included in the survey, and a note is included to specify the new questions that were added to wave 2:

- 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) (a new question was added in wave 2 specific to 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 because of risk of infection (a new question was added in wave 2 specific to possible contamination and infection)
- The fact that dilation of the eye before an aflibercept injection is not necessary (a new question was added and administered to physicians who indicate that the patient's eye should be dilated prior to an aflibercept injection to determine what guides this decision)
- 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 also included the following items to investigate physician receipt and use of the prescriber educational materials:

- Receipt and review of the Summary of Product Characteristics (SmPC), 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 (new question in wave 2)
- 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 (a new question was added in wave 2 to collect reasons for not providing the booklet)

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

- Physicians' focus within ophthalmology
- Physicians' practice setting (new question in wave 2)
- Average number of anti-VEGF intravitreal injections the physician administers each month
- Average number of aflibercept injections the physician administers each month (new question in wave 2)

- Timing of last aflibercept injection
- Years in practice
- Gender
- Age (new question in wave 2)

Annex 2 contains the questionnaire.

9.5 Data sources and measurement

The source of information for the study was self-reported data collected from physicians using a standard questionnaire with closed-ended response choices.

The physician questionnaire was drafted using best practices for instrument development. The questions were tailored to the study aims and the information provided in the educational materials. Additional questions were included to obtain information needed to assess potential differences across subgroups and identify biases (e.g., demographics, experience prescribing and administering aflibercept).

To thoroughly evaluate the questionnaire before fielding wave 1, the questionnaire was tested through cognitive interviews with physicians in France, Germany, Italy, Spain, and the UK. The pretest interviews helped to identify problems with questionnaire items, wording, and response choices, and ensured that participants understood the questions. The cognitive testing helped to 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.

9.6 Bias

In any observational study, researchers must address the potential for biases, particularly if there is a possibility that the respondents are not representative of the target population. Likewise, the potential for intervention effects and/or response error may present additional sources of bias. Efforts were made to both minimize and identify potential sources of bias in this study as described below.

As noted above, the physician questionnaire was cognitively pretested prior to wave 1 data collection in order to identify any problems with the questionnaire items, wording, and response choices, and to ensure consistency across cultures and languages. The questionnaire was modified based on feedback from the cognitive interviews with physicians. This process helped to ensure that the questions measured the appropriate concepts consistently and accurately across all countries, and thus was intended to minimize bias in responses.

The physician survey was administered as an online questionnaire. Physicians were not able to go back to previous questions. This kept them from changing their answers based on subsequent questions. The level of missing data was minimal; most participants who began the survey completed all items of the questionnaire.

Although a comparison of participating physician characteristics with nonparticipating physicians was not possible within the panel recruitment framework, the diversity of physician characteristics and experience with aflibercept in the final sample gave some assurance that the target population was well represented. However, despite efforts to ensure a representative sample of physicians, participants may have differed from nonparticipants on key characteristics measured in the questionnaire (e.g., knowledge, reading the educational materials). The direction and magnitude of such potential bias is not known.

9.7 Study size

The target size for the wave 2 physician survey was 60 to100 physicians per country, for a total of 300 to 500 physicians. With a study size of 100 physician responses for a given question, the maximum width of an exact 95% confidence interval (CI) around the percentage who responded correctly is 20.3%, and 60 responses gives a maximum width of 26.4%. Ultimately, the number of completed physician surveys included 100 surveys from France, 57 from Germany, 79 from Italy, 99 from Spain, and 119 from the UK, for a total of 454 completed surveys.

9.8 Data transformation

Derived variables were created for each of the six knowledge questions (i.e., questions 10, 11, 12, 15, 20, and 21) that asked the respondent to "select all that apply" and had more than one correct response; these variables indicated the number of correct responses selected.

9.9 Statistical methods

All analyses were performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, North Carolina). No formal hypothesis testing was conducted. Version 1.0 of the statistical analysis plan is provided as a stand-alone document referenced in Annex 1, Table 1-1, of this report.

9.9.1 Main summary measures

Data analyses were descriptive in nature and focused primarily on summarizing the questionnaire responses. Summary tables consisting of frequencies with percentages were created for all questionnaire responses. Response distribution percentages for a question were based on the total number of respondents who had an opportunity to answer the question. This total excluded those who were asked to skip because of an answer given in a prior question (skip pattern). The sum of respondents who were asked to skip was listed in a row labelled "Not applicable skip pattern" under the question, with no percentage calculated for that row. The counts of respondents who had an opportunity but did not answer were included in a row labelled "No answer" with a calculated percentage.

9.9.2 Main statistical methods

The analysis population consisted of respondents who were eligible for the study, provided informed consent, and completed at least one knowledge question in full.

Questionnaire items were divided into the following categories: (1) physician experience with aflibercept, (2) physician characteristics, (3) physician knowledge, (4) physician receipt and use of aflibercept educational materials, (5) physician ratings of aflibercept education materials, and (6) physician use of patient booklet. Separate analysis tables for each category were generated to display the response distributions of all questions, for the overall set of respondents as well as broken out by country.

In addition, the knowledge questions were stratified by the following variables to explore the association between each variable and physician knowledge levels:

- Question 23: time since last reviewed the Eylea Prescriber Guide (< 1 week ago, between 1 week and 3 months ago, more than 3 months ago, I don't know, did not review Eylea Prescriber Guide)

- Question 28: the physicians' focus within ophthalmology (retina only or in combination with any other response, general ophthalmology only, any other response either alone or in combination)
- Question 28a: practice setting (office-based only, hospital-based only, office and hospital-based only, mobile unit and/or other only)
- Question 29a: the average number of monthly Eylea injections (< 5, 5-20, 21-40, 41-100, > 100)
- Question 31: physicians' years in practice (5 years or fewer, 6-10 years, 11-15 years, 16-20 years, 21-25 years, more than 25 years)
- Question 32: physicians' sex (male, female, I prefer not to answer)
- Question 32a: the physicians' age in years (20-39 years, 40-49 years, 50-59 years, ≥ 60 years, I prefer not to answer)
- Whether or not the physician was part of the wave 1 analysis population

A formal set of analysis tables was created for each of the two stratification variables showing the greatest impact on knowledge: (1) focus within ophthalmology and (2) average number of aflibercept injections per month. These two stratifications are also discussed when summarizing the knowledge results in subsequent sections. A general summary of the results for each of the eight stratification variables listed above is provided in Section 10.5.1.

Exact 95% CIs around the percentage of physicians that answered each knowledge question correctly were generated using the Clopper-Pearson method. These CIs were calculated for the overall and by-country result tables but not for the additional stratified tables.

Annex 3 includes tables presenting the complete set of knowledge question results overall and by country. Annex 4 includes tables presenting results by other stratification variables.

9.9.3 Missing values

No imputation of missing values was performed.

9.9.4 Sensitivity analyses

Not applicable

9.9.5 Amendments to the statistical analysis plan

Not applicable

9.10 Quality control

This project was conducted in accordance with internal standard operating procedures (SOPs) of participating institutions. The PPD Office of Quality Assurance, an independent unit that reports to the Executive Vice President of PPD oversaw quality assurance for this study.

PPD followed our established quality management system to conduct this study including the following:

- Training of PPD staff
- Ensuring data protection and integrity
- Collecting, analyzing, and managing data

- Maintaining records
- Performing vendor qualification, quality control, and quality-review activities

PPD SOPs were used to guide the conduct of the study. These procedures included 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.

PPD Office of Quality Assurance qualified Kantar as an approved vendor (via on-site audit in 2017) before this study was initiated. Kantar has been a trusted partner and has been continuously qualified throughout the duration of this study without interruption.

In accordance with relevant PPD SOPs, quality-control activities were performed throughout the project. This included the following activities:

- The initial programmer reviewed all program log files for errors and warning messages and retained electronic copies of all final log files in the project folder.
- The programmer accounted for the number of observations reported at each executed data step and noted in the program code when the number of observations increased or decreased. A second programmer independently wrote program code and confirmed the findings of the initial programmer.
- A quality-control checklist has been maintained for the project, and a hard copy was printed, signed, and retained in the project folder.
- All key study documents, such as the analysis plan, questionnaires, and study reports underwent quality-control review, senior scientific review, and editorial review.

Versions of SOPs and records of quality-review and quality-control activities used throughout the course of a study are maintained and available with the study records.

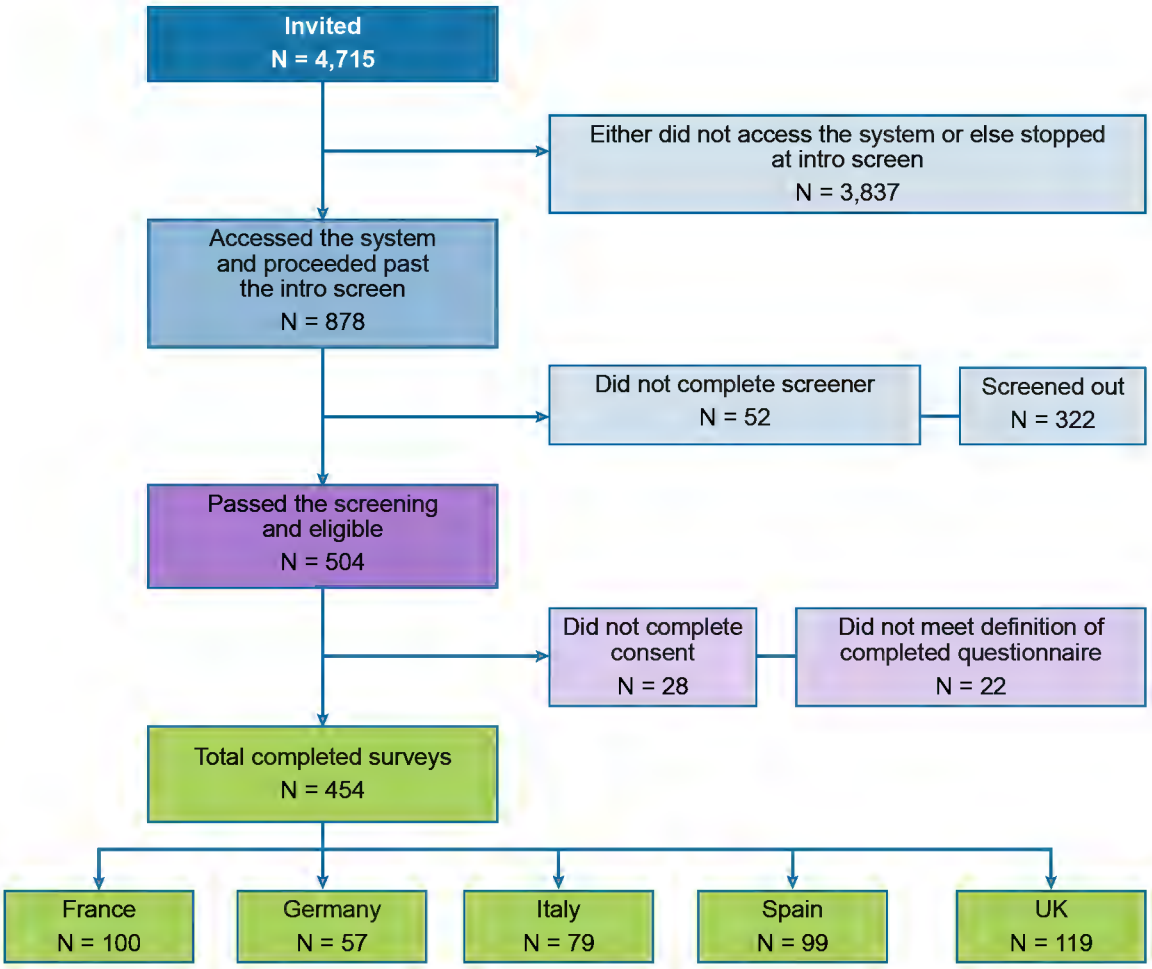
10. Results

10.1 Participants

A total of 4,715 physicians were invited to participate in the survey. Of those, 878 physicians accessed the survey, continued past the introduction screen, and reached the screening questions. Of the physicians who reached the screening questions, 504 completed the three questions and were eligible, 52 did not complete the screening questions, and 322 were ineligible because they had not prescribed aflibercept nor administered an aflibercept injection in the preceding 6 months. Of the 504 physicians eligible, 28 physicians did not consent to participate and 22 did not meet the definition for a completed questionnaire (i.e., did not answer at least one knowledge question). The remaining 454 physicians completed the questionnaire and are included in this analysis. The overall response rate was 9.6%.

Because of the limited number of potentially eligible physicians on the panel, wave 2 included a mix of new participants and physicians who previously also participated in wave 1. Of the 454 physicians in the final sample, 107 physicians (24%) also participated in the previous administration of the survey (specifically, 18% of physicians in France were repeat responders, 16% in Germany, 37% in Italy, 24% in Spain, and 23% in the UK).

Figure 1 presents the disposition of physicians invited to participate.



UK = United Kingdom.

Figure 1: Disposition of Physician Invited to Participate

10.2 Descriptive data

Physicians were asked to indicate their focus within ophthalmology (multiple responses were allowed) and their responses included retina (63%), general ophthalmology (57%), glaucoma (26%), and cataract (34%). The majority of physicians (74%) characterized their practice as hospital based. Physicians most commonly reported having been treating patients for 6 to 10 years (23%), 11 to 15 years (21%) and 16 to 20 years (20%). About two-thirds of the physicians (67%) were male. More than half of physicians (60%) were aged 40 to 59 years, while 27% were younger than 40 years and 7% were 60 years or older. Table 1 provides characteristics of the participating physicians.

Table 1: Physician and practice characteristics

Question	Number of Physicians (%)					
	France n = 100	**Germany n = 57**	**Italy n = 79**	**Spain n = 99**	**UK n = 119**	**Overall N = 454**
Focus within ophthalmology[a]						
Retina	66 (66)	35 (61)	43 (54)	60 (61)	83 (70)	287 (63)
General ophthalmology	55 (55)	41 (72)	44 (56)	54 (55)	63 (53)	257 (57)
Glaucoma	28 (28)	24 (42)	25 (32)	22 (22)	21 (18)	120 (26)
Cataract	38 (38)	27 (47)	21 (27)	33 (33)	36 (30)	155 (34)
Other	2 (2)	5 (9)	10 (13)	6 (6)	6 (5)	29 (6)
No answer	0 (0)	2 (4)	0 (0)	4 (4)	1 (1)	7 (2)
Practice setting where intravitreal injections are performed[a]						
Office-based	40 (40)	41 (72)	27 (34)	16 (16)	19 (16)	143 (31)
Hospital-based	69 (69)	18 (32)	58 (73)	86 (87)	106 (89)	337 (74)
Mobile unit	1 (1)	0 (0)	2 (3)	1 (1)	1 (1)	5 (1)
Other	4 (4)	1 (2)	5 (6)	1 (1)	0 (0)	11 (2)
No answer	0 (0)	2 (4)	0 (0)	4 (4)	1 (1)	7 (2)
Years treating patients						
5 years or fewer	13 (13)	8 (14)	9 (11)	13 (13)	14 (12)	57 (13)
6 to 10 years	35 (35)	9 (16)	10 (13)	22 (22)	27 (23)	103 (23)
11 to 15 years	14 (14)	12 (21)	15 (19)	28 (28)	25 (21)	94 (21)
16 to 20 years	13 (13)	17 (30)	20 (25)	18 (18)	24 (20)	92 (20)
21 to 25 years	12 (12)	6 (11)	9 (11)	9 (9)	17 (14)	53 (12)
More than 25 years	13 (13)	3 (5)	15 (19)	5 (5)	10 (8)	46 (10)
No answer	0 (0)	2 (4)	1 (1)	4 (4)	2 (2)	9 (2)
Age						
20-29 years	2 (2)	0 (0)	1 (1)	0 (0)	4 (3)	7 (2)
30-39 years	40 (40)	12 (21)	8 (10)	26 (26)	31 (26)	117 (26)
40-49 years	20 (20)	21 (37)	22 (28)	41 (41)	42 (35)	146 (32)
50-59 years	23 (23)	14 (25)	33 (42)	21 (21)	34 (29)	125 (28)
60-69 years	12 (12)	3 (5)	12 (15)	3 (3)	3 (3)	33 (7)
70 years or older	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)

Question	Number of Physicians (%)					
	France n = 100	Germany n = 57	Italy n = 79	Spain n = 99	UK n = 119	Overall N = 454
I prefer not to answer	3 (3)	5 (9)	2 (3)	3 (3)	4 (3)	17 (4)
No answer	0 (0)	2 (4)	1 (1)	4 (4)	1 (1)	8 (2)
Sex						
Male	79 (79)	38 (67)	58 (73)	47 (47)	80 (67)	302 (67)
Female	20 (20)	12 (21)	19 (24)	42 (42)	30 (25)	123 (27)
I prefer not to answer	1 (1)	5 (9)	1 (1)	6 (6)	8 (7)	21 (5)
No answer	0 (0)	2 (4)	1 (1)	4 (4)	1 (1)	8 (2)

UK = United Kingdom.
[a] This was a “tick all that apply” question; thus, the sum of responses is greater than 100%.

Per the screening criteria, all physicians had prescribed (94%) and/or administered (78%) aflibercept in the past 6 months for indications including: wet age-related macular degeneration (93%) and/or visual impairment due to diabetic macular edema (81%), macular edema secondary to central retinal vein occlusion (72%), macular edema secondary to branch retinal vein occlusion (67%), and myopic choroidal neovascularization (50%).

Nearly half of the physicians (44%) reported administering an average of 5 to 40 anti-VEGF injections per month, and 39% reported administering more than 40 anti-VEGF injections per month. About half of physicians (53%) reported administering 5 to 40 aflibercept injections per month, while just over a quarter (27%) of physicians reported administering more than 40 aflibercept injections per month. Most physicians (76%) had administered their last aflibercept injection less than 1 month ago.

Table 2 provides information on physicians’ experience with aflibercept.

Table 2: Physicians’ experience with aflibercept

Question	Number of Physicians (%)					
	France n = 100	Germany n = 57	Italy n = 79	Spain n = 99	UK n = 119	Overall N = 454
Have you prescribed Eylea and/or administered an Eylea injection to a patient in the past 6 months? (Screener question 1)[a]						
Prescribed aflibercept	97 (97)	55 (96)	69 (87)	93 (94)	114 (96)	428 (94)
Administered an aflibercept injection	87 (87)	44 (77)	51 (65)	68 (69)	102 (86)	352 (78)
For which of the following indications have you prescribed and/or administered Eylea in the past 6 months? (Screener question 2)[a]						
wAMD	93 (93)	52 (91)	68 (86)	93 (94)	114 (96)	420 (93)
CRVO	89 (89)	39 (68)	37 (47)	67 (68)	97 (82)	329 (72)
DME	88 (88)	45 (79)	50 (63)	83 (84)	100 (84)	366 (81)
BRVO	77 (77)	36 (63)	37 (47)	58 (59)	97 (82)	305 (67)
Myopic CNV	51 (51)	23 (40)	41 (52)	50 (51)	60 (50)	225 (50)

Question	Number of Physicians (%)					
	France n = 100	**Germany n = 57**	**Italy n = 79**	**Spain n = 99**	**UK n = 119**	**Overall N = 454**
How many anti-VEGF intravitreal injections do you administer on average each month? (Question 29)						
Fewer than 5 per month	9 (9)	13 (23)	14 (18)	22 (22)	14 (12)	72 (16)
5 to 20 per month	19 (19)	14 (25)	26 (33)	25 (25)	26 (22)	110 (24)
21 to 40 per month	23 (23)	9 (16)	18 (23)	18 (18)	22 (18)	90 (20)
41 to 100 per month	32 (32)	10 (18)	16 (20)	20 (20)	38 (32)	116 (26)
More than 100 per month	17 (17)	9 (16)	5 (6)	10 (10)	18 (15)	59 (13)
No answer	0 (0)	2 (4)	0 (0)	4 (4)	1 (1)	7 (2)
How many Eylea injections do you administer on average each month? (Question 29a)						
Fewer than 5 per month	9 (9)	14 (25)	18 (23)	24 (24)	18 (15)	83 (18)
5 to 20 per month	35 (35)	19 (33)	34 (43)	37 (37)	27 (23)	152 (33)
21 to 40 per month	22 (22)	9 (16)	16 (20)	13 (13)	27 (23)	87 (19)
41 to 100 per month	26 (26)	9 (16)	9 (11)	19 (19)	29 (24)	92 (20)
More than 100 per month	8 (8)	3 (5)	2 (3)	2 (2)	17 (14)	32 (7)
No answer	0 (0)	3 (5)	0 (0)	4 (4)	1 (1)	8 (2)
When did you last administer an Eylea injection? (Question 30)						
Less than 1 month ago	89 (89)	37 (65)	59 (75)	72 (73)	90 (76)	347 (76)
1 to 3 months ago	4 (4)	11 (19)	9 (11)	11 (11)	19 (16)	54 (12)
4 to 6 months ago	5 (5)	4 (7)	5 (6)	8 (8)	3 (3)	25 (6)
I don’t know	2 (2)	3 (5)	6 (8)	4 (4)	6 (5)	21 (5)
No answer	0 (0)	2 (4)	0 (0)	4 (4)	1 (1)	7 (2)

BRVO = branch retinal vein occlusion; CNV = choroidal neovascularization; CRVO = central retinal vein occlusion; DME = diabetic macular edema; UK = United Kingdom; VEGF = vascular endothelial growth factor; wAMD = wet age-related macular degeneration.

[a] This question was "tick all that apply."

10.3 Outcome data

Not applicable

10.4 Main results

In the following sections, we present the complete set of results from the physicians who completed the questionnaire. The results are organized in the following categories: (1) physician knowledge, (2) receipt and use of aflibercept educational materials, (3) ratings of aflibercept education materials, and (4) use of patient booklet.

First, we describe the results, question by question, for the overall sample and by country. For the knowledge questions, we also describe the results by stratification variables that appeared to have the largest impact: (1) number of aflibercept injections performed per month and (2) the physicians' focus within ophthalmology. After discussing each of the questions individually, we also present an overall summary of each of the stratification variables across all knowledge questions in Section 10.5.1.

Annex 3 includes tables presenting the complete response distributions to all of the survey questions for physicians overall and by country. Annex 4 includes tables presenting response distributions to all knowledge questions stratifying by: (1) number of aflibercept injections performed per month and (2) the physicians' focus within ophthalmology.

10.4.1 Knowledge

Storage and preparation

Sixty-eight percent of physicians correctly identified the incorrect statement "Eylea is a suspension, which contains particulates and is cloudy"; 83% correctly responded that a "30-gauge x ½-inch injection needle should be used"; and 92% correctly responded that "adequate anaesthesia and asepsis (e.g., use of povidone iodine) must be provided for the patient" (Figure 2).

For the response "Eylea is a suspension, which contains particulates and is cloudy," knowledge was highest in Germany and the UK (77%), and ranged from 59% to 66% in each of the other three countries. For the response "30-gauge x ½-inch injection needle should be used," knowledge was particularly high in Germany (89%) and ranged from 75% to 87% in the other countries. Knowledge regarding "adequate anaesthesia and asepsis (e.g., use of povidone iodine) must be provided for the patient" was high across all countries, ranging from 89% to 94% (Annex 3, Table 3-1; questions 1a, 1h, 1i).

For all three of these questions, there was a positive trend between the number of aflibercept injections physicians performed per month and the proportion of correct responses. For example, for the question about Eylea containing particulates and being cloudy, the proportion of correct responses increased from 53% for physicians who performed fewer than five injections per month, to 63% for physicians who performed 5 to 20 per month, to 70% for physicians who performed 21 to 40 per month, to 84% for physicians who performed 41 to 100 per month, and to 91% for those who performed over 100 (Annex 4, Table 3-1a; questions 1a, 1h, 1i).

Physicians who indicated that their focus within ophthalmology included "retina" had the highest proportion of correct responses for all three of these questions, and the proportion of correct responses for physicians who indicated their focus was only general ophthalmology was 5% to 23% lower on these questions. All remaining categories combined (including cataract, glaucoma, other, or general ophthalmology in combination with one of those categories) (n = 59) had the lowest proportions of correct responses on these questions (15%

to 40% lower than those who focused on the retina) (Annex 4, Table 3-1b; questions 1a, 1h, 1i).

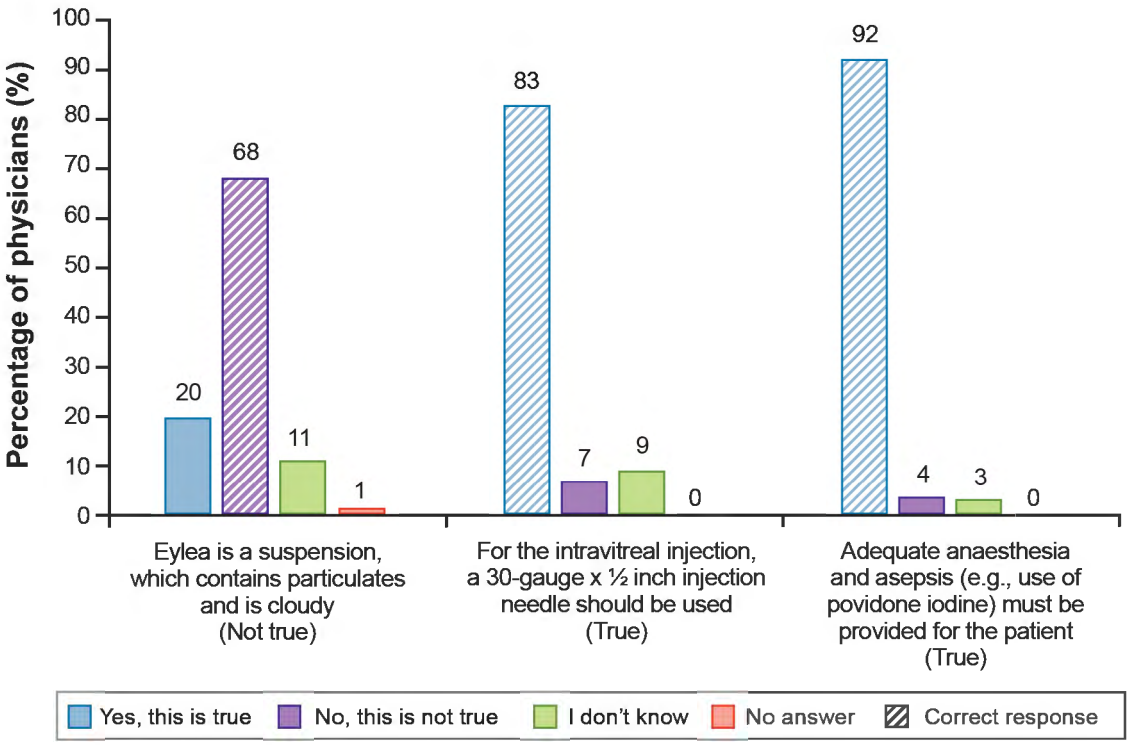


Figure 2: For each of the following statements related to the storage and preparation of Eylea, please indicate if the statement is true, not true, or if you do not know. (questions 1a, 1h, 1i) (N = 454)

Eighty-three percent of physicians correctly identified that the statement "the vial of Eylea is reusable between patients and can be used for multiple injections" as false; 84% correctly indicated that use of more than one injection from the vial can lead to contamination and subsequent infection; 85% correctly responded that the vial should be stored in the refrigerator; and 44% correctly identified the statement "prior to usage, the vial of Eylea may be kept at room temperature for up to 48 hours" as inaccurate (the actual duration is up to 24 hours) (Figure 3).

Physician knowledge was similar across countries for the question regarding whether the vial was reusable between patients (84%-93% correct) and that multiple uses can lead to contamination and subsequent infection (85%-91% correct), with the exception of Spain (65% and 73%, respectively). Knowledge across countries was also similar for the question regarding whether the vial should be stored in the refrigerator (82%-93% correct). Physicians from the UK (50%) and Italy (46%) more often identified the inaccurate statement about whether the vial may be kept at room temperature for up to 48 hours when compared with physicians from the other countries (37%-42%) (Annex 3, Table 3-1; questions 1c, 1e, 1g, 1k).

There was a clear trend between the number of injections physicians performed per month and the proportion of correct responses for each of these four questions. The correct response proportion for the question regarding whether the vial was reusable generally increased, with 77% for physicians who performed fewer than five injections per month responding correctly and 94% for those who performed over 100 injections per month responding correctly.

Similarly for the question regarding multiple uses and contamination and infection, the correct response proportion increased from 73% for physicians who performed fewer than five injections per month to 94% for those who performed over 100 injections per month. Likewise, correct response proportions increased from 75% to 97% across the same stratification groups for whether the vial should be stored in the refrigerator. The proportion of correct responses was fairly consistent across the stratification groups for identifying the inaccurate statement about keeping the vial at room temperature (Annex 4, Table 3-1a; questions 1c, 1e, 1g, 1k).

Physicians who indicated that their focus included “retina” had the highest proportion of correct responses for all four of these questions, and physicians with other primary focuses had noticeably lower proportions of correct responses (Annex 4, Table 3-1b; questions 1c, 1e, 1g, 1k).

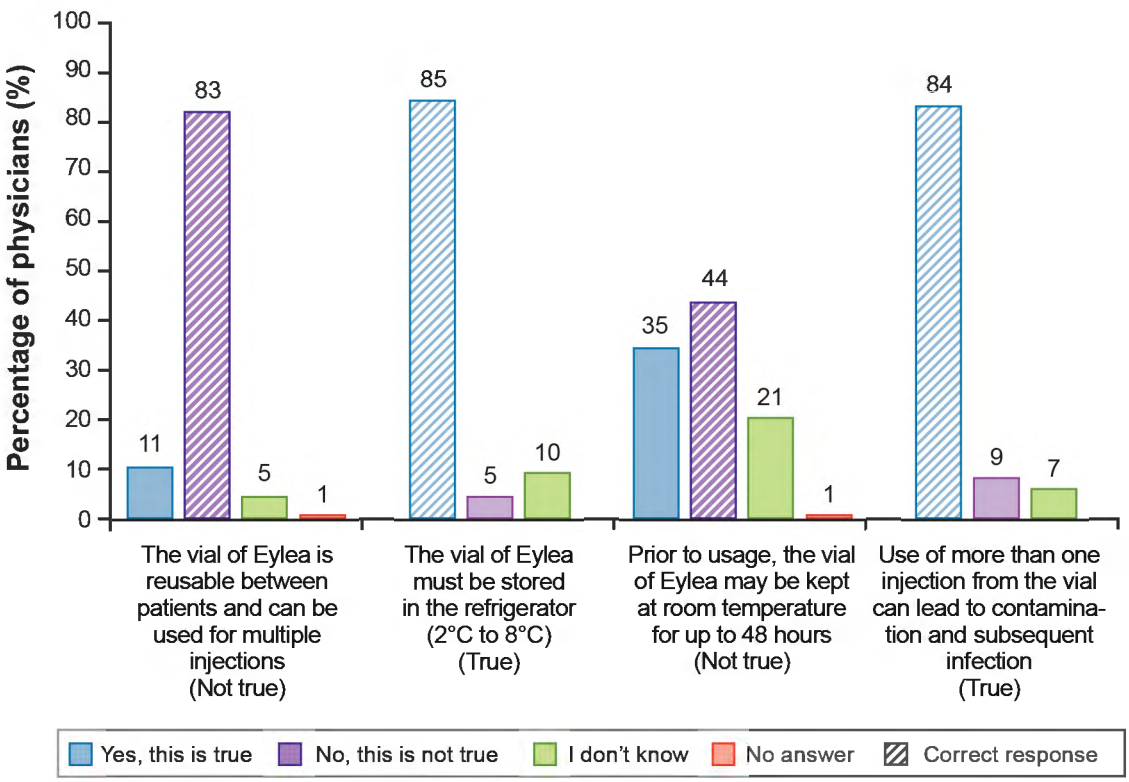


Figure 3: For each of the following statements related to the storage and preparation of Eylea, please indicate if the statement is true, not true, or if you do not know. (questions 1c, 1e, 1g, 1k) (N = 454)

Dosing

Recommended dose for aflibercept

When presented with three questions concerning dosing recommendations, most physicians (78%) correctly responded that "50 microlitres (2 mg)" was the recommend dose for aflibercept (Table 3). The proportion of correct responses varied across countries, with Italy and the UK having the highest proportion of correct responses at 85% and 82%, respectively, and the other countries ranging from 68% to 77%.

The proportion of correct responses was relatively high regardless of the number of aflibercept injections performed per month (ranging from 72% to 81%) (Annex 4, Table 3-2a; question 2). Physicians whose focus included retina and those who indicated their focus was general ophthalmology only, each had an 80% correct response proportion, while the combined category of all other focuses was lower at 61% (Annex 4, Table 3-2b; question 2).

Table 3: Recommended dose for aflibercept

Question	Number of Physicians (%)					
	France n = 100	Germany n = 57	Italy n = 79	Spain n = 99	UK n = 119	Overall N = 454
What is the recommended dose for Eylea? (Question 2)						
12.5 microlitres (0.5 mg)	19 (19)	4 (7)	4 (5)	12 (12)	15 (13)	54 (12)
50 microlitres (2 mg)[a]	68 (68)	44 (77)	67 (85)	76 (77)	98 (82)	353 (78)
90 microlitres (3.6 mg)	3 (3)	2 (4)	5 (6)	1 (1)	0 (0)	11 (2)
100 microlitres (4 mg)	6 (6)	3 (5)	3 (4)	4 (4)	2 (2)	18 (4)
I don't know	4 (4)	4 (7)	0 (0)	6 (6)	4 (3)	18 (4)

[a] Correct response.

Excess volume of Aflibercept

Eighty-two percent of physicians correctly identified the statement "The Eylea vial contains more than the recommend dose of Eylea and excess volume should be expelled before injection" as true. Fifty-eight percent correctly responded that the plunger of the syringe should be depressed until the tip aligns with the 0.05 mL line on the syringe (Table 4).

For the question regarding the vial containing more than the recommended dose, the proportion of correct responses was high (84%-92%) among the physicians from France, Germany, and the UK, and it was noticeably lower in Italy and Spain (75% and 73%, respectively). There was a clear trend between the number of injections physicians performed per month and the proportion of correct responses. Physicians who performed fewer than five injections per month had the lowest correct response proportion (67%), and those who performed over 100 injections per month had the highest (100%) (Annex 4, Table 3-2a; question 8). Physicians whose focus included retina had a higher proportion of correct responses (89%) than either those whose focus was general ophthalmology only (71%) or all other categories combined (76%) (Annex 4, Table 3-2b; question 8).

For the question regarding the tip aligning with the 0.05 mL line, the correct response proportions were 76% for the UK and 70% for France, but were substantially lower at 44% for each of the other three countries (Table 4). Again there was a clear trend with knowledge level increasing with number of injections performed per month. The correct response proportion increased from 36% for physicians who performed fewer than five injections per month, to 53% for physicians who performed 5 to 20 per month, to 63% for physicians who performed 21 to 40 per month, to 78% both for physicians who performed 41 to 100 per month, as well for those who performed more than 100 (Annex 4, Table 3-2a; question 9). Physicians whose focus included the retina had the highest correct response proportion (64%), followed by those whose focus was general ophthalmology only (55%), and then all other categories combined (37%) (Annex 4, Table 3-2b; question 9).

Table 4: Excess volume of aflibercept

Question	Number of Physicians (%)					
	France n = 100	Germany n = 57	Italy n = 79	Spain n = 99	UK n = 119	Overall N = 454
The Eylea vial contains more than the recommended dose of Eylea, and excess volume should be expelled from the syringe before injecting. (Question 8)						
True [a]	92 (92)	48 (84)	59 (75)	72 (73)	103 (87)	374 (82)
False	5 (5)	6 (11)	15 (19)	22 (22)	9 (8)	57 (13)
I don't know	3 (3)	3 (5)	5 (6)	4 (4)	6 (5)	21 (5)
No answer	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	2 (0)
After removing all of the drug from the Eylea vial with a syringe, the plunger of the syringe should be depressed until the tip aligns with the line that marks which number of milliliters (mL) on the syringe? (Question 9)						
0.05 mL [a]	70 (70)	25 (44)	35 (44)	44 (44)	91 (76)	265 (58)
0.1 mL	9 (9)	8 (14)	6 (8)	16 (16)	6 (5)	45 (10)
0.15 mL	1 (1)	4 (7)	5 (6)	6 (6)	2 (2)	18 (4)
0.2 mL	6 (6)	4 (7)	13 (16)	6 (6)	4 (3)	33 (7)
0.5 mL	8 (8)	5 (9)	8 (10)	12 (12)	10 (8)	43 (9)
I don't know	6 (6)	11 (19)	12 (15)	14 (14)	5 (4)	48 (11)
No answer	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	2 (0)

UK = United Kingdom.
[a] Correct response.

Safe Use

Preparing the patient for treatment

Physicians were asked to tick all statements that apply in response to the question, "What should you do to prepare the patient before the start of treatment with Eylea?" (Figure 4). Three correct responses were listed among the options and overall; the proportion correct was highest for "inform the patient to report any signs and symptoms…" (94%) and "explain the implications of anti-VEGF treatment" (90%); a smaller proportion of the physicians selected "provide the patient booklet …" (67%).

Across countries, the correct response proportions were similar for "inform the patient to report any signs and symptoms…" ranging from 89% to 98%. For the statement "explain the implications of anti-VEGF treatment," they were more than 90% in France, Germany, and the UK; 85% in Spain, and 76% in Italy. For the statement "provide the patient booklet …," the proportion of correct responses was consistent across countries (52%-65%) with the exception of the UK, where 88% selected the correct response (Annex 3, Table 3-3; question 10).

There appeared to be a slight association between number of injections performed per month and proportion of correct responses to these questions, with higher numbers of injections for the most part showing slightly higher knowledge, but the association was not as strong as seen with many of the other questions, probably largely because there was little room for variation as the correct response rates were so high for these questions (Annex 4, Table 3-3a; question

10). There were fairly large differences in the correct response proportion based on physician focus within ophthalmology. Physicians whose focus included the retina had the highest correct response proportion, followed by those whose focus was general ophthalmology, and then all other categories combined (Annex 4, Table 3-3b; question 10).

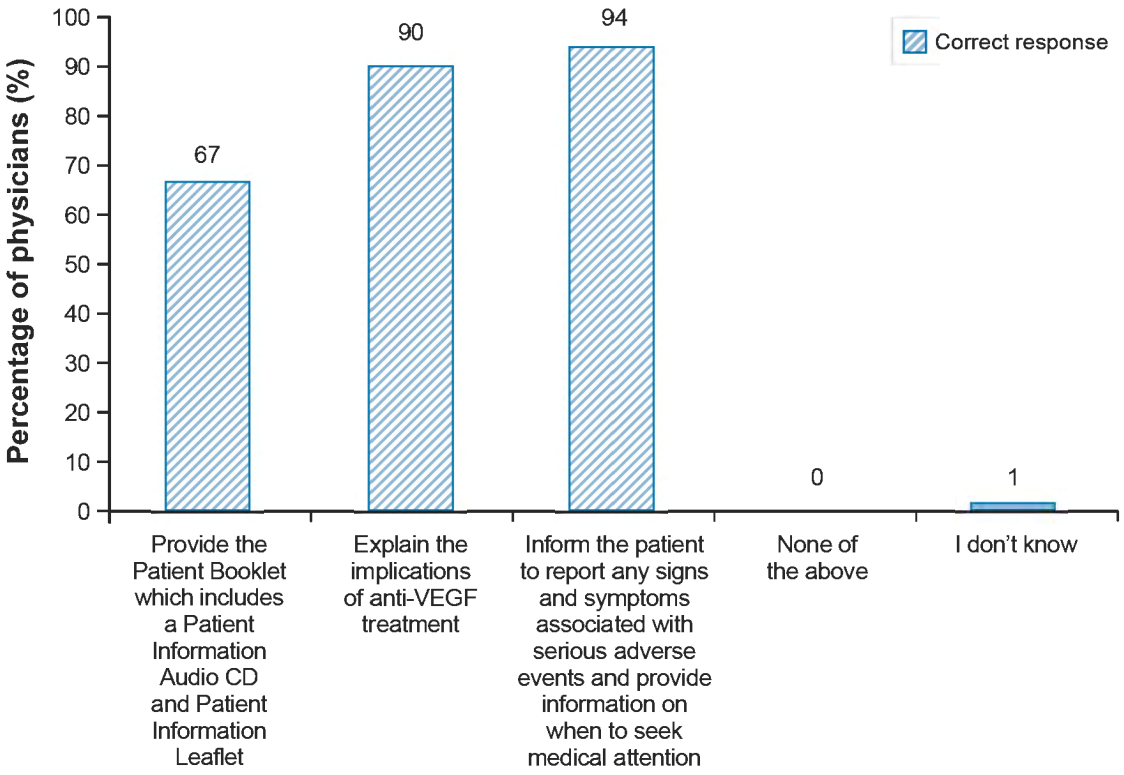


Figure 4: What should you do to prepare the patient before the start of treatment with Eylea? Tick all that apply. (question 10) (N = 454)

Contraindications

Physicians were asked to identify the contraindications for aflibercept (Figure 5). Overall, knowledge was high with the proportion of correct responses ranging from 82% for "patients with active severe intraocular inflammation" to 92% for hypersensitivity. The proportions of correct responses were similar across countries, except for the response "patients with active severe intraocular inflammation," which 90% of the physicians from Spain selected correctly; the other 4 countries ranged from 77% to 81% (Annex 3, Table 3-3; question 11). Minor trends were evident between higher number of injections per month and increased level of correct responses to this question (Annex 4, Table 3-3a; question 11). Physicians whose focus within ophthalmology included the retina and those whose focus was general ophthalmology did quite similarly on all three of these, while all other categories combined had noticeably lower knowledge (Annex 4, Table 3-3b; question 11).

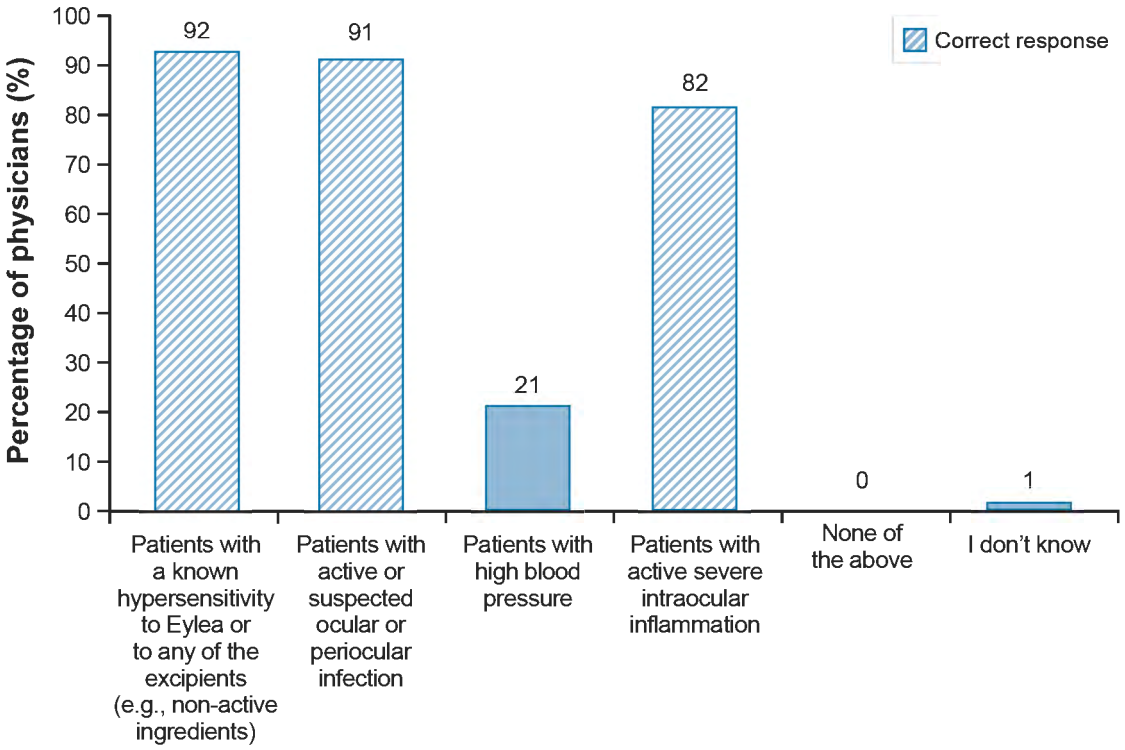


Figure 5: Eylea is contraindicated in which of the following patients? Tick all that apply. (question 11) (N = 454)

Use in women of childbearing potential

Physicians were asked about the recommended use of aflibercept in women of childbearing potential (Figure 6). Overall, 53% of physicians correctly responded that "women of childbearing potential must use effective contraception …" Fifty-eight percent of physicians correctly reported that "Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk, and 28% (6% of whom also selected the correct response) reported a conservative option that Eylea should "never be used in pregnancy." Germany had the highest proportion correct (63%) on the response related to "effective contraception," followed by Spain (59%). France, Italy, and the UK were all lower, ranging from 47% to 50%. The UK had the highest proportion correct (69%) on the response related to "unless the potential benefit outweighs the potential risk," followed by Spain (60%). France, Germany, and Italy were lower, ranging from 49% to 53% (Annex 3, Table 3-3; question 12). There we no apparent trends between knowledge and number of injections per month (Annex 4, Table 3-3a; question 12. The physicians' focus within ophthalmology appeared to have much less association with knowledge levels for this question (Annex 4, Table 3-3b; question 12).

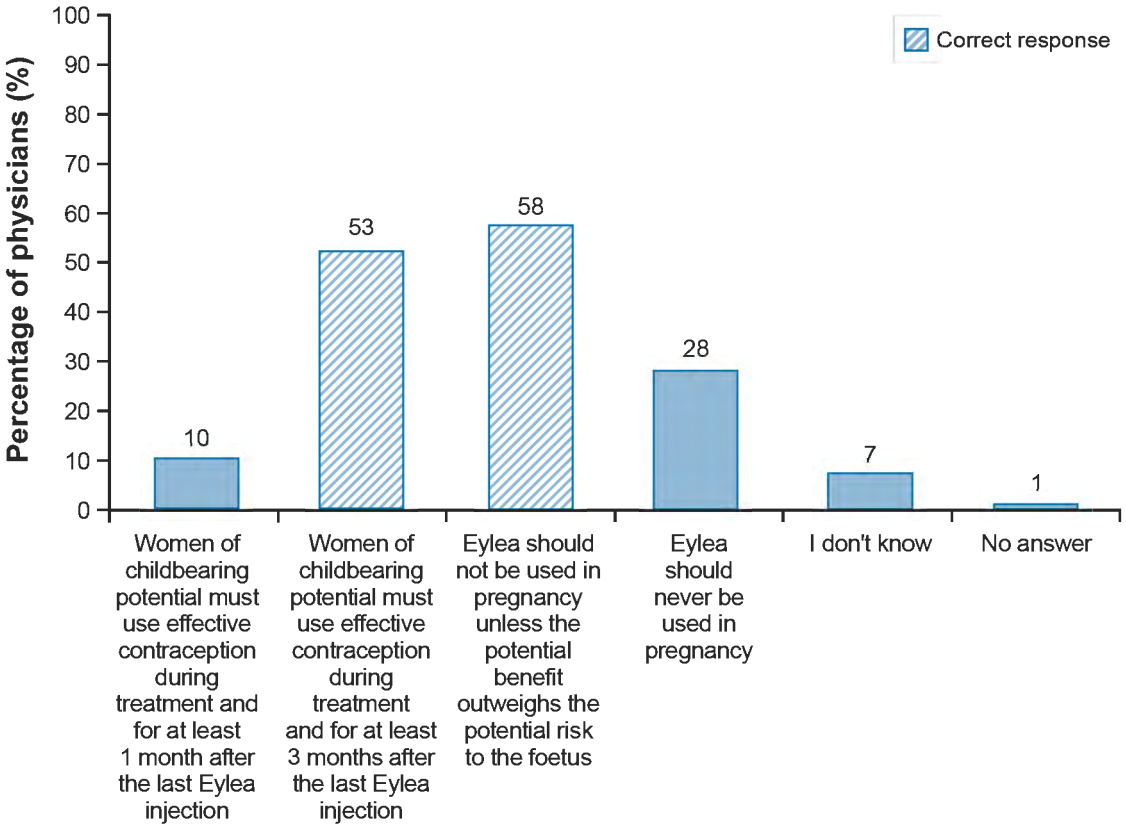


Figure 6: What are the recommendations for use of Eylea in women of childbearing potential and for use in pregnancy? Tick all that apply. (question 12) (N = 454)

The question, "What is the recommendation regarding Eylea use and breastfeeding?" was added for the wave 2 administration of the Eylea physician survey. Seventy-six percent of respondents selected the correct response, "Eylea is not recommended during breastfeeding" (Figure 7). Germany had the highest proportion to select the correct response (84%), and the UK and France had the lowest at 71% and 73%, respectively (Annex 3, Table 3-3; question 12a). There were no apparent trends between knowledge and number of injections per month (Annex 4, Table 3-3a; question 12a). The physicians' focus within ophthalmology did not appear to be associated with knowledge levels for this question (Annex 4, Table 3-3b; question 12a).

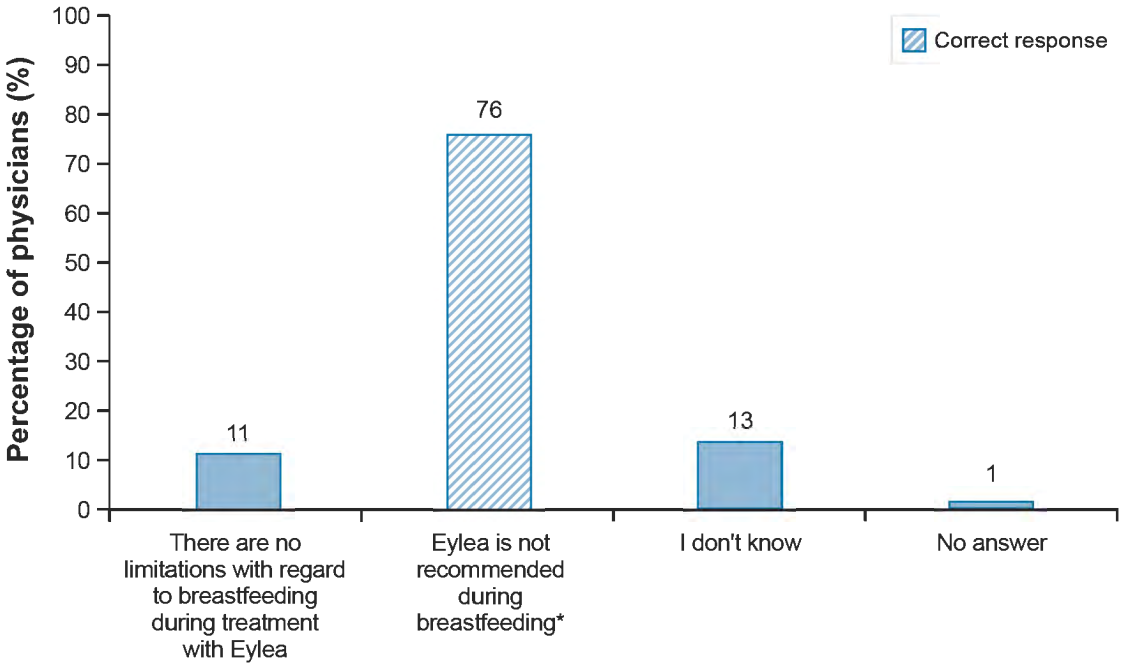


Figure 7: What is the recommendation regarding Eylea use and breastfeeding? (question 12a) (N = 454)

Injection Procedure

Physicians were asked a series of six questions about proper injection procedures (Figure 8 and Figure 9). Overall, physicians' knowledge of this topic was high.

The majority of physicians (89%) correctly confirmed that topical anesthesia should be used prior to the aflibercept injection. Likewise, 92% of physicians correctly identified as true the statement "a disinfectant (e.g., povidone iodine solution) should be applied to the periocular skin, eyelid, and ocular surface."

When asked to identify steps that should be taken before marking the scleral injection site, most of the physicians correctly selected "cover the eye with a sterile drape" (84%) and "insert a sterile lid speculum" (76%). In addition, 22% of physicians indicated that "dilate the eye" is a step that should be taken prior to injection ("dilate the eye" is not a correct response).

More than three-quarters (77%) of the physicians correctly responded that the eye should be marked at a distance 3.5 to 4.0 mm posterior to the limbus in preparation for the aflibercept injection. Similarly, 80% correctly responded that the injection needle should be inserted into the vitreous cavity, avoiding the horizontal meridian and aiming toward the center of the globe (Annex 3, Table 3-4; questions 13-17).

Knowledge was consistently high across countries for use of topical anesthesia, ranging from 75% in Germany to 96% in the UK. Likewise, knowledge was high for applying disinfectant (87% in Spain to 98% in France). Knowledge was also high across countries for covering the eye with a sterile drape (83% in the UK to 97% in France), with the exception of Italy (66%). The UK (86%) and France (80%) had a high proportion of correct responses for "insert a sterile lid speculum"; whereas knowledge in the other countries was lower (65% in Spain to 72% in Italy). Knowledge that the eye should be marked at a distance 3.5 to 4.0 mm posterior to the limbus varied from 61% and 69% in Germany and Spain, respectively, to 78% in Italy, 81% in France, and 87% in the UK. Knowledge of how the needle should be inserted into the

eye was high in France (88%) and the UK (87%), and somewhat lower in Germany (67%), Spain (72%), and Italy (76%).

For all five of these questions, there were trends between a higher number of injections per month and increased knowledge. For the question related to the "location where the eye should be marked," the proportion of correct responses ranged from 57% for the lowest injection category to 97% for the highest, and for the question about where the needle should be inserted, the proportion of correct responses ranged from 59% for the lowest injection category to 97% for the highest (Annex 4, Table 3-4a; questions 13-17). For all five questions, the physicians whose focus was on the retina had correct response proportions at least 10% higher than one or both of the other two stratification groups (Annex 4, Table 3-4b; questions 13-17).

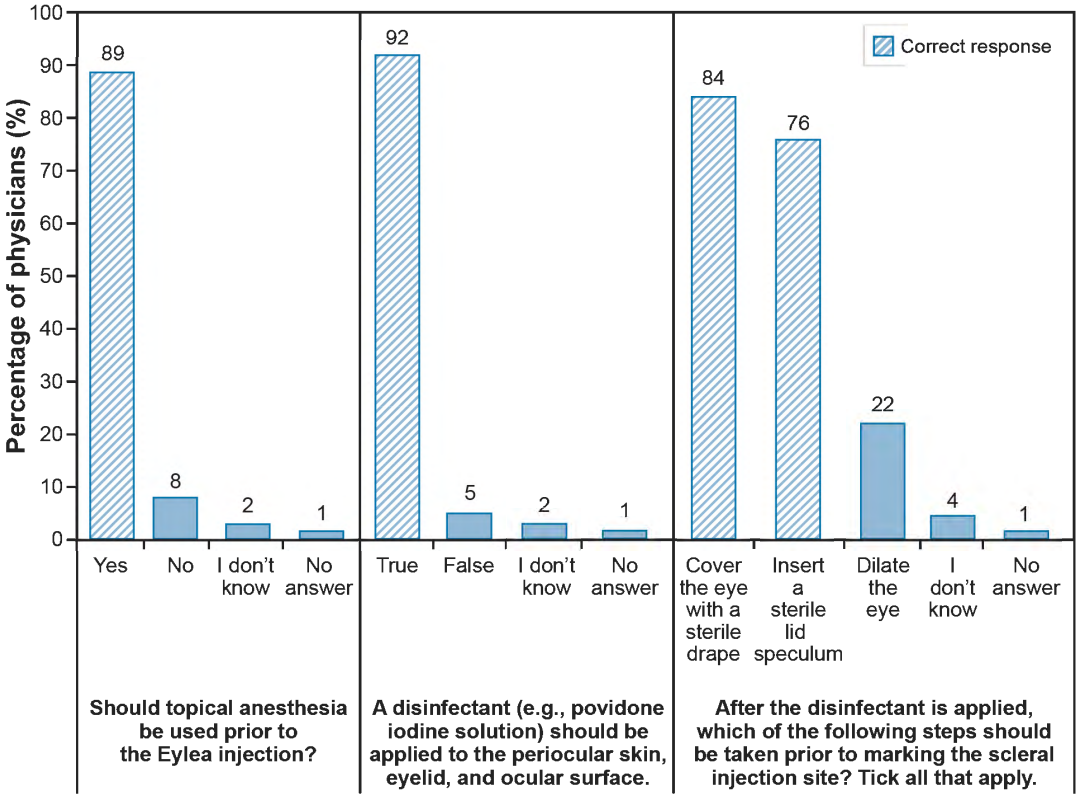


Figure 8: Questions 13, 14, and 15 (N = 454)

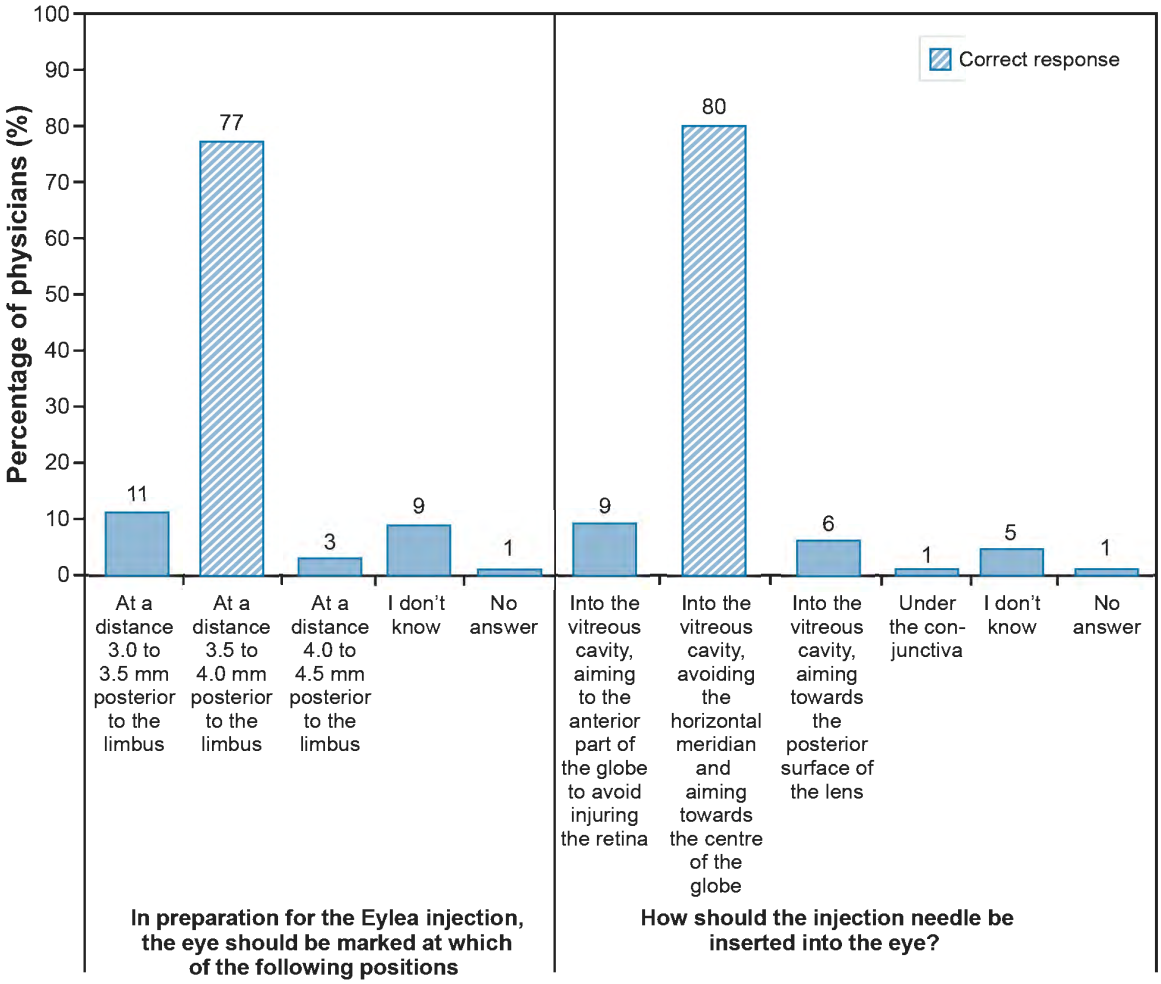


Figure 9: Questions 16 and 17 (N = 454)

A follow-up question (15a) was added to wave 2 of the survey to gather additional information from the physicians who selected "dilate the eye" in response to question 15, "After the disinfectant is applied, which of the following steps should be taken prior to marking the scleral injection site? Tick all that apply." Among the 22% of physicians (N = 102) who selected "dilate the eye," the following were the reasons given:

- Eye dilation is done for regular assessment of the underlying disease or other assessments (e.g., fundus examination) (58%)
- Requirements/recommendations by national or local guidelines for intravitreal injections, local protocols, or other recommendations (54%)
- Personal preference/judgment (41%)
- Eye dilation is done in conjunction with imaging procedure(s) (26%)
- Eye dilation is not done routinely but rather upon medical judgment for each individual patient, as needed and dictated by the clinical context (25%)
- Information in the Eylea educational materials (23%)
- None of the above (3%)

Side effects

When asked how physicians should evaluate a patient's vision immediately after an aflibercept injection, 54% of physicians correctly responded "by hand movements or counting fingers" and 13% responded "using a standard eye chart" (a more rigorous method than the correct response). There was remarkable variability in correct responses across countries, with the UK having the highest proportion of correct responses (79%), followed by Germany (65%), France (64%), Spain (37%), and Italy (18%) (Annex 3, Table 3-5; question 18). There was also a clear, strong trend between the number of injections physicians performed per month and the proportion of correct responses, increasing from 30% for physicians who performed fewer than five injections per month, to 46% for physicians who performed 5 to 20 per month, to 62% for physicians who performed 21 to 40 per month, to 76% for physicians who performed 41 to 100 per month, to 81% for those who performed more than 100 (Annex 4, Table 3-5a; question 18). Physicians whose focus within ophthalmology included the retina had the highest correct response proportion (63%), and those who indicated their focus was general ophthalmology only and all the combined category of all other focuses was much lower at 40% and 41%, respectively (Annex 4, Table 3-5b; question 18).

Most physicians (83%) correctly identified the statement "an increase in intraocular pressure has been seen within 60 minutes after an injection with Eylea" as true. The proportion of correct responses ranged from 75% in Spain to 95% in Germany (Annex 3, Table 3-5; question 19). Again, there was an overall positive trend, with knowledge increasing with number of injections per month from 77% in physicians who averaged less than five injections per month to 91% for those who performed over 100 (Annex 4, Table 3-5a; question 19). Physicians whose focus within ophthalmology included the retina had the highest correct response proportion (89%), followed by those who indicated their focus was general ophthalmology (82%), and then by the combined category of all other focuses (69%) (Annex 4, Table 3-5b; question 19).

Figure 10 shows the response distributions to these questions.

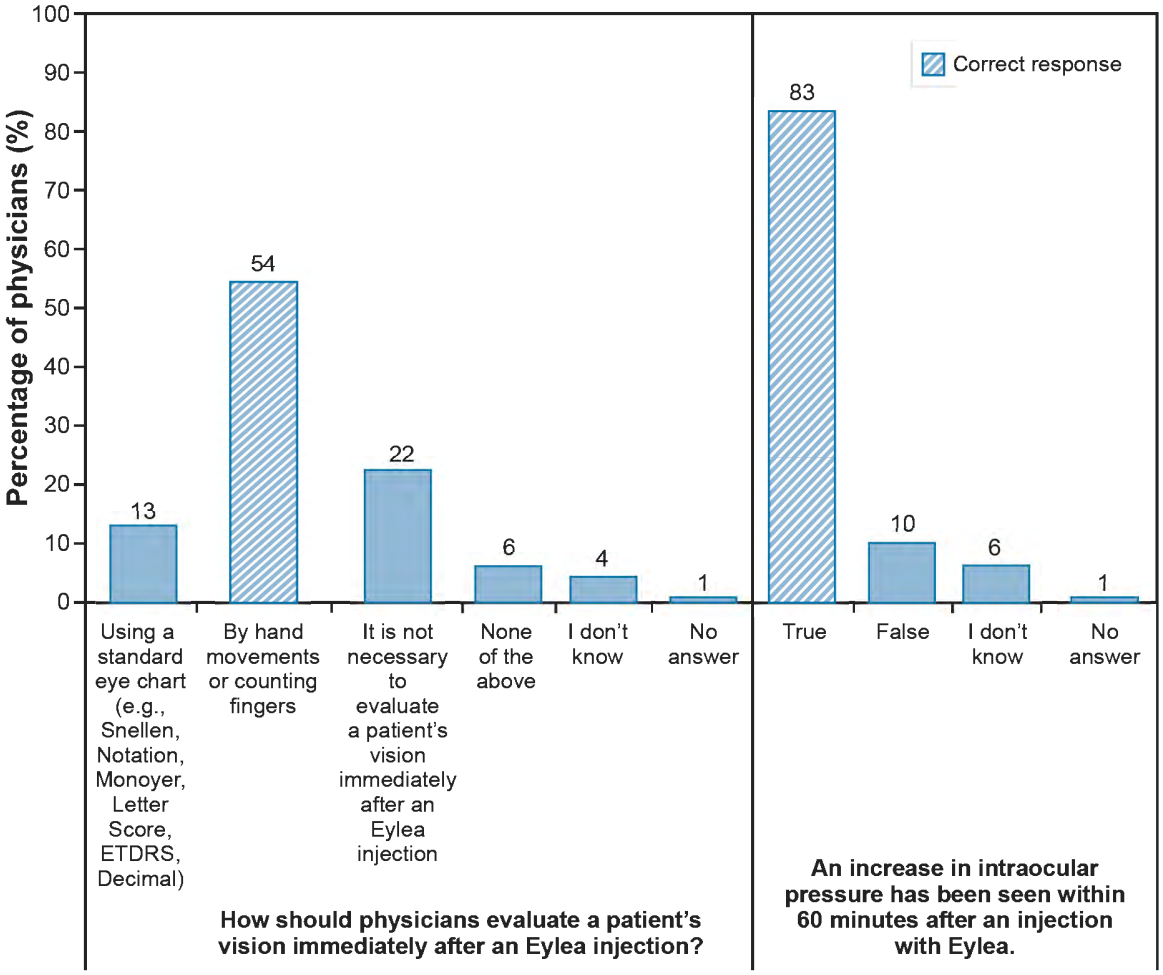


Figure 10: Questions 18 and 19 (N = 454)

Physicians were asked to tick all statements that apply in response to what they should do "in relation to the potential of increased intraocular pressure immediately following an Eylea injection" (Figure 11). Fifty-six percent of physicians correctly responded "ensure that sterile equipment is available to perform paracentesis if necessary," and 62% of physicians correctly responded "monitor patients after the injection procedure (e.g., tonometry or check for perfusion of the optic nerve head)." Knowledge was high in the UK for both these responses (71% and 70%, respectively) but was much lower in several of the other countries, with the lowest being 40% in Spain for the first item and 42% in France for the second item (Annex 3, Table 3-5; question 20). There was no apparent association between physicians' knowledge of these topics and the number of injections performed per month (Annex 4, Table 3-5a; question 20). Physician focus within ophthalmology had less of a strong association with knowledge on this question (Annex 4, Table 3-5b; question 20).

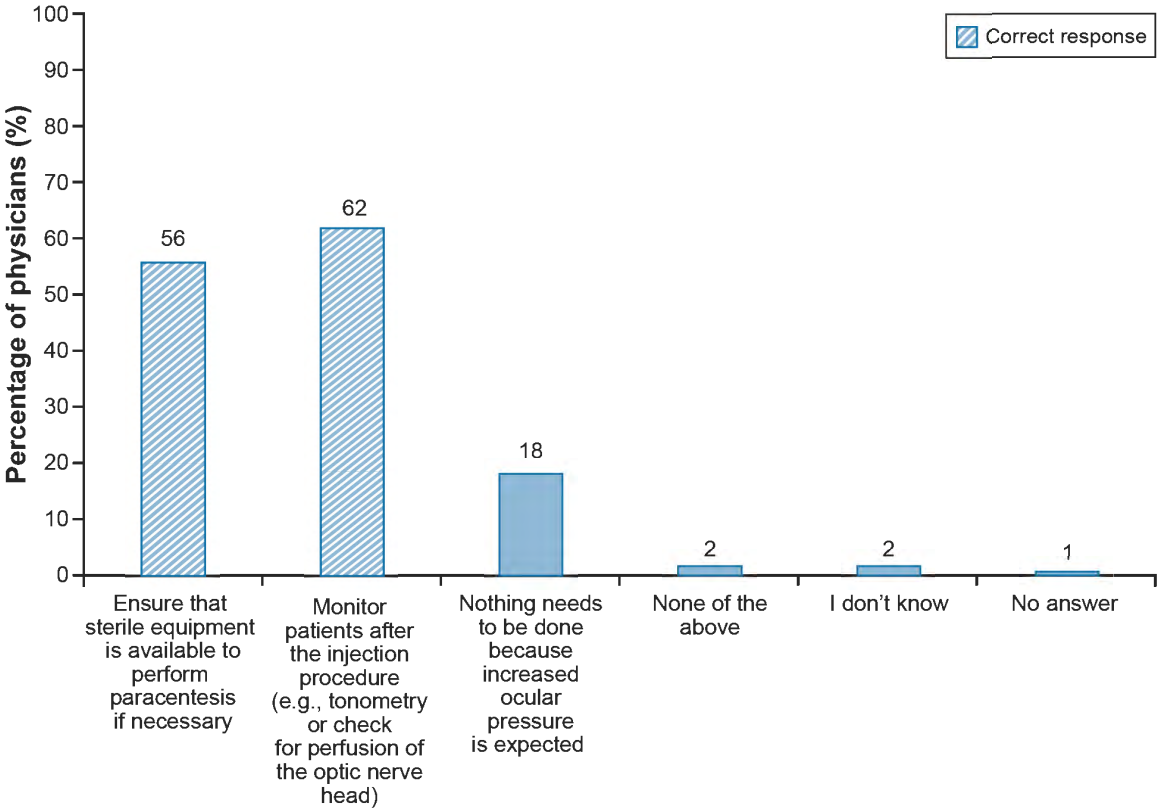


Figure 11: What should physicians do in relation to the potential of increased intraocular pressure immediately following an Eylea injection? Tick all that apply. (question 20) (N = 454)

Physicians were asked to tick all statements that apply in response to the question, "after the Eylea injection, patients should be instructed to report, without delay, any symptoms and suggestive of which of the following conditions" (Figure 12). Overall, a high proportion of physicians correctly ticked "intraocular inflammation" (81%) and "endophthalmitis" (87%). Knowledge ranged from 72% (Italy) to 86% (France and Germany) across countries for "intraocular inflammation," and from 77% (Germany) to 95% (UK) for "endophthalmitis" (Annex 3, Table 3-5; question 21). There was a slight trend between higher number of injections per month and higher knowledge for both of these side effects (Annex 4, Table 3-5a; question 21). The correct response proportions were similar for physicians whose focus was on the retina and those who focused on general ophthalmology only and a lower for the "all other categories of focus combined" group (Annex 4, Table 3-5b; question 21).

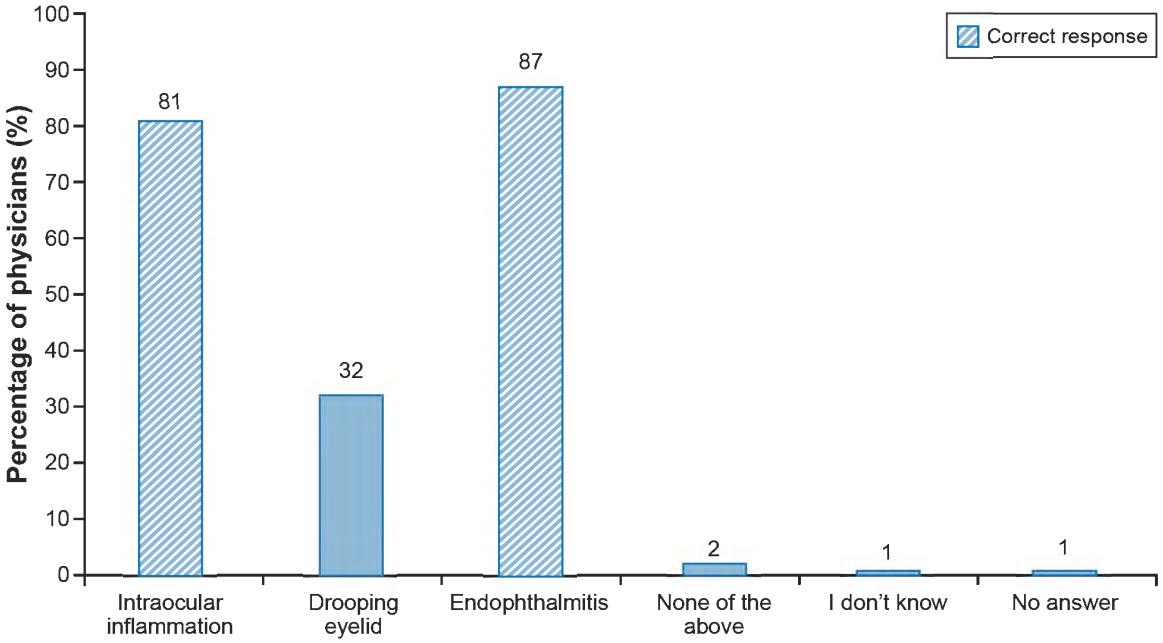


Figure 12: After the Eylea injection, patients should be instructed to report, without delay, any symptoms suggestive of which of the following conditions? Tick all that apply. (question 21) (N = 454)

Physicians were given a list of potential signs, symptoms, or diagnoses that are known undesirable side effects of aflibercept injection (Figure 13). The following are the percentages of physicians that correctly selected each of the potential signs or symptoms: transient increased intraocular pressure (92%), endophthalmitis (91%), tear or detachment of the retinal pigment epithelium (70%), and cataract (traumatic, nuclear, subcapsular, cortical) or lenticular opacities (69%). Seventy-four percent of physicians correctly identified that fever was not a potential related side effect and 51% correctly identified that headaches were not a potential related side effect.

Physicians from the UK and France tended to have the highest knowledge on this series of questions about side effects, while those from Italy, Spain, and Germany tended to have noticeably lower knowledge (Annex 3, Table 3-5; question 22). Except for "fever" and "transient increased intraocular pressure," there were not particularly strong trends between number of injection performed per month and correct response. For "fever," the correct response proportions ranged from 57% for the fewer than five injections per month category to 88% for the more than 100 per month category, and for "transient increased intraocular pressure," correct response proportions increased from 87% to 97% as the number of injections per month increased (Annex 4, Table 3-5a; question 22). Physicians whose focus included the retina had the highest correct response proportion for all of these questions (Annex 4, Table 3-5b; question 22).

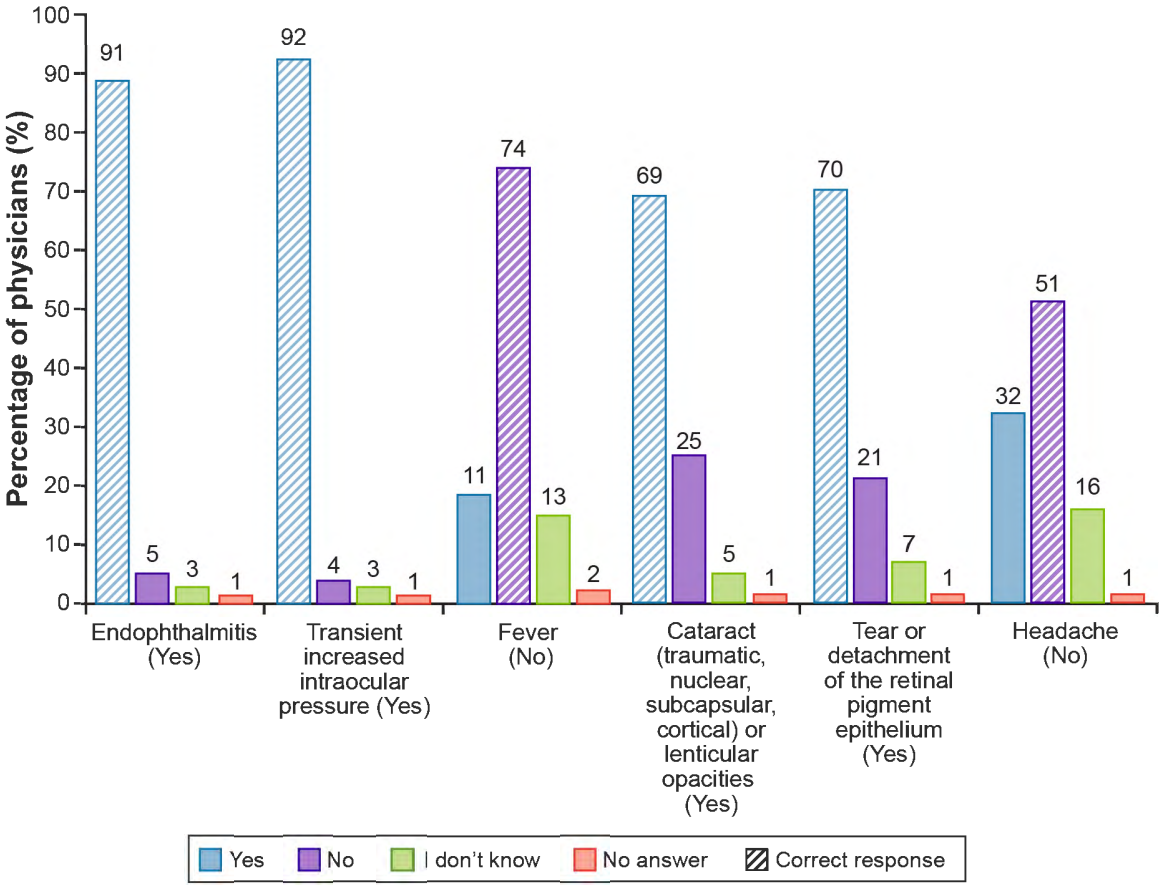


Figure 13: Which of the following signs, symptoms, or diagnoses are known undesirable side effects of using Eylea? (question 22) (N = 454)

10.4.2 Physician Receipt and Use of Aflibercept Educational Materials (Annex 3, Table 4; question 23)

Before the wave 2 survey, Bayer updated the educational materials for aflibercept and following member-state approval distributed the revised materials to physicians in all countries according to the locally approved distribution plan. In general, the educational materials sent to physicians included the aflibercept prescriber guide, injection procedure video, SmPC, patient booklet, audio CD, and patient information leaflet. Data collection was initiated at least 3 months after distribution of materials to allow time for physicians to have received the revised prescriber guide.

Physicians participating in the study were asked to indicate whether or not they received and reviewed aflibercept educational materials (Table 5).

The majority of physicians (89%) reported receiving the SmPC; of those, 83% indicated they reviewed it. The proportions of reported receipt and review were similar across countries.

Most physicians (82%) reported receiving the prescriber guide; of those, 82% indicated they reviewed it. The reported rate of receipt ranged from 73% in Spain to 91% in Italy. Among those who said they received the prescriber guide, reported review of the guide ranged from 79% in Spain to a high of 90% in Germany.

Just more than half of physicians (54%) reported receiving the intravitreal injection procedure video; of those, 72% indicated they reviewed it. The proportion of reported receipt ranged from 46% in Spain to 60% in Germany.

Finally, 65% reported receiving the indication-specific patient booklet, including a patient booklet audio CD and patient information leaflet; of those, 70% indicated they reviewed it. The proportion of receipt of the patient booklet varied noticeably; from 47% in Spain to 76% in the UK.

Table 5: Receipt and review of materials (question 23)

Question	Number of Physicians (%)					
	France n = 100	**Germany n = 57**	**Italy n = 79**	**Spain n = 99**	**UK n = 119**	**Overall N = 454**
Summary of Product Characteristics						
Received	89 (89)	51 (89)	76 (96)	88 (89)	102 (86)	406 (89)
Reviewed[a]	75 (84)	47 (90)	62 (82)	73 (79)	86 (83)	343 (83)
Eylea Prescriber Guide						
Received	87 (87)	48 (84)	72 (91)	72 (73)	94 (79)	373 (82)
Reviewed[a]	70 (80)	44 (90)	60 (83)	59 (79)	77 (81)	310 (82)
Intravitreal injection procedure video						
Received	56 (56)	34 (60)	45 (57)	46 (46)	64 (54)	245 (54)
Reviewed[a]	34 (61)	26 (74)	40 (87)	33 (66)	50 (75)	183 (72)
Indication-Specific Patient Booklet including a patient information audio CD and the Patient Information Leaflet						
Received	64 (64)	42 (74)	50 (63)	47 (47)	91 (76)	294 (65)
Reviewed[a]	37 (58)	30 (70)	40 (78)	32 (63)	71 (77)	210 (70)

[a] Percentages are calculated among those physicians who either answered “yes” or who did not provide an answer to “Have you received the material?”

A new question was added to query the physicians who indicated that they had reviewed the Eylea Prescriber Guide to find out how long ago they reviewed it (Table 6). Most physicians (66%) indicated that it had been more than 3 months since they reviewed it, and the second most common answer was between 1 week and 3 months ago at 24%. There was considerable variability by country.

Table 6: Time since reviewed Eylea prescriber guide

Question	Number of Physicians (%)					
	France n = 100	Germany n = 57	Italy n = 79	Spain n = 99	UK n = 119	Overall N = 454
Approximately how long ago did you review the Eylea Prescriber Guide? (question 23e)						
Less than 1 week ago	4 (6)	1 (2)	7 (12)	4 (7)	2 (3)	18 (6)
Between 1 week and 3 months ago	7 (10)	17 (39)	16 (27)	20 (34)	13 (17)	73 (24)
More than 3 months ago	54 (77)	21 (48)	34 (57)	34 (58)	61 (79)	204 (66)
I don't know	5 (7)	5 (11)	3 (5)	1 (2)	1 (1)	15 (5)
Not applicable skip pattern (did not review Eylea Prescriber Guide)	30	13	19	40	42	144

10.4.3 Physician ratings of aflibercept education materials (Annex 3, Table 5; question 24)

Physicians were asked to rate the materials that they had previously indicated reviewing on a scale from 1 (not at all helpful) to 4 (extremely helpful).

Among physicians who reported reviewing each item, a rating of 3 or more was given to the SmPC by 81% of physicians; to the prescriber guide by 85% of physicians, to the intravitreal injection procedure video by 81% of physicians, to the patient booklet by 83% of physicians, to the patient booklet audio CD by 73% of physicians, and to the patient information leaflet by 86% of physicians.

Across all countries, at least 70% of physicians who reviewed each of the materials rated that material at least 3, with the exception of the patient information audio CD.

10.4.4 Physician use of patient booklet

Physicians were asked, "considering the patients under your care who are receiving Eylea injections, to how many did you provide an Eylea Patient Booklet?" (Table 7) (Annex 3, Table 6, question 27). The majority of physicians selected either "all of my patients" (37%), or "most of my patients" (24%), although 16% selected "none of my patients." Across countries, the distribution of responses was variable; with only 48% in France and 54% in Spain responding "all of my patients" or "most of my patients," compared with higher percentages in the other countries (58% to 77%).

Table 7: Physician use of Eylea patient booklet

Question	Number of Physicians (%)					
	France n = 100	**Germany n = 57**	**Italy n = 79**	**Spain n = 99**	**UK n = 119**	**Overall N = 454**
Considering the patients under your care who are receiving Eylea injections, to how many did you provide an Eylea Patient Booklet? (question 26)						
All of my patients	20 (20)	24 (42)	34 (43)	33 (33)	56 (47)	167 (37)
Most of my patients	28 (28)	9 (16)	17 (22)	20 (20)	36 (30)	110 (24)
Half of my patients	5 (5)	7 (12)	5 (6)	5 (5)	7 (6)	29 (6)
A few/some of my patients	19 (19)	7 (12)	12 (15)	21 (21)	11 (9)	70 (15)
None of my patients	28 (28)	9 (16)	11 (14)	16 (16)	8 (7)	72 (16)
No answer	0 (0)	1 (2)	0 (0)	4 (4)	1 (1)	6 (1)

In a new tick all that apply question added to this wave of the survey, the 63% of physicians (N = 287) who indicated that they did not provide the patient booklet to "all of my patients" were asked why they did not (Annex 3, Table 6, question 26a). The most frequent responses were:

- I provide the same information from the Eylea patient booklet to patients verbally and give them the chance to ask questions (46%)
- I did not receive enough copies of the Eylea patient booklet to distribute to all my Eylea patients (38%)
- I provide alternate materials (e.g., treatment consent form) (35%)
- I do not provide the Eylea patient booklet to patients who cannot read or have cognitive limitations (28%)
- I do not provide the Eylea patient booklet to patients with a language barrier (21%)
- I am concerned that the Eylea patient booklet may scare patients (14%)
- I do not feel that the Eylea patient booklet is helpful to patients (10%)

Among physicians who indicated that they provided the patient booklet to at least some of their patients, more than 90% responded that they provide it "before the start of treatment with Eylea" (Table 8) (Annex 3, Table 6, question 27). This was consistent across all countries, ranging from 88% to 95%.

Table 8: Physicians' timing of Eylea patient booklet distribution

Question	Number of Physicians (%)					
	France n = 100	**Germany n = 57**	**Italy n = 79**	**Spain n = 99**	**UK n = 119**	**Overall N = 454**
When would you provide the Patient Booklet and discuss it with your patient? (question 27) Tick all that apply.						
Before the start of treatment with Eylea	64 (89)	42 (88)	63 (93)	74 (89)	106 (95)	349 (91)
When a patient has an Eylea-related adverse event	9 (13)	7 (15)	4 (6)	7 (8)	4 (4)	31 (8)
I do not reference the Patient Information Booklet	6 (8)	2 (4)	3 (4)	4 (5)	2 (2)	17 (4)
Other	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	2 (1)
No answer	0 (0)	1 (2)	0 (0)	4 (5)	1 (1)	6 (2)
Not applicable skip pattern (selected "None of my patients" for question 26)	28	9	11	16	8	72

10.5 Other analyses

10.5.1 Stratified knowledge results

This section provides a general summary of the knowledge question results by each of the stratification variables that were explored. As opposed to the previous section where the results of the key stratification variables (country, number of injections, and focus in ophthalmology) are presented on a question-by-question basis, this section assesses the general impact of each stratification variable across the entire set of knowledge questions.

Country

We observed variability in the proportions of correct responses across countries. Some differences could be explained by the composition of participants within each country. For example, 70% of physicians in the UK versus 54% of physicians in Italy reported that their focus within ophthalmology was retina. Additionally, 39% of physicians in the UK versus 14% of physicians in Italy reported administering 40 or more aflibercept injections per month.

Average number of aflibercept injections performed per month

There was a clear trend, with physicians who performed more aflibercept injections per month consistently providing more correct responses than those who performed lower volumes of injections. This trend was consistent across the five categories representing increasing injection numbers. The complete set of knowledge questions stratified by average monthly injections can be found in Annex 4, Table 3-1a-Table 3-5a.

Focus in ophthalmology

Ophthalmologists who indicated they focused on the retina had the highest proportions of correct responses on all knowledge questions, followed by those who indicated their focus was general ophthalmology only. The combined category of all other areas of focus had notably lower correct response proportions. The complete set of knowledge questions stratified by focus in ophthalmology can be found in Annex 4, Table 3-1b-Table 3-5b.

Sex

Physician sex did not seem to be associated with knowledge level; knowledge across males and females was within 10% on almost every question.

Age

There was some association between physician age and knowledge, but it was not a consistent pattern. Physicians aged 20 to 39 years and physicians 60 years and older responded similarly to each other and had noticeably higher knowledge than the other age categories, 40 to 49 years and 50 to 59 years.

Time since reviewed prescriber guide

There was some association between time since reviewed prescriber guide and knowledge, but there was not a consistent pattern. Those who said they reviewed the prescriber guide more than 3 months ago demonstrated the highest knowledge. The category with second highest knowledge included those who reviewed the prescriber guide less than a week ago, followed by those who reviewed it between 1 week and 3 months ago. Those who never reviewed it had significantly lower knowledge than all of the other response categories.

Years treating patients as an ophthalmologist

Physicians with the least experience treating patients (i.e., 5 or fewer years) had much lower knowledge than the other categories. Beyond that, there was not a clear trend across the other duration categories, although those with the most years treating patients (i.e., 21 or more years) demonstrated slightly higher knowledge than the intermediate categories.

Practice setting

Those physicians who indicated they were both office- and hospital-based physicians (n = 45) had the highest correct response proportion on most of the knowledge questions. The hospital-based only physicians (n = 291) had the next highest correct response proportions, followed closely by those who were office-based only (n = 95). The 13 respondents who indicated they worked from a mobile unit and/or selected “other” had noticeably lower knowledge than the other categories.

Repeaters and nonrepeaters

On almost all of the questions, physicians in the wave 2 survey who participated in a previous administration (i.e., repeaters) had higher correct response proportions than those who were participating in the survey for the first time (i.e., nonrepeaters); although the differences between the two groups were 10% or less for two-thirds of the questions.

10.5.2 Comparison of results across waves

The analysis of wave 1 survey included 428 respondents, and the analysis of wave 2 included 454 respondents; included in those final study sizes are 107 physicians who participated in both waves.

Annex 5 provides a graphical summary of survey response distributions across the two waves. The sex and years in practice of respondents was consistent across survey administrations, as

was whether they had prescribed and/or administered aflibercept and how recently they last administered an aflibercept injection, with the majority of each wave last administering an injection within the past month. The indications that physicians reported prescribing for were also similar across waves, with the exception of myopic choroidal neovascularization, an indication which was approved in the EU at the end of 2015. Fewer physicians selected "retina" as a particular focus within ophthalmology in wave 2 (63%) compared with wave 1 (74%). More respondents on wave 2 (68%) compared with wave 1 (54%) indicated they were the primary person responsible for the preparation of the aflibercept injection. Physicians in wave 2 reported performing slightly higher anti-VEGF intravitreal injection volume, with 39% reporting more than 40 per month, compared with 33% for wave 1.

Physicians' knowledge was quite similar across the waves of the survey, with the responders in wave 1 of the survey more often having just slightly higher correct response proportions. For the majority of questions, the difference in correct response proportions were no more than 5% to 6%. A few questions that stood out as having larger differences included "After the disinfectant is applied, which of the following steps should be taken prior to marking the scleral injection site?", Eighty-eight percent of wave 1 respondents correctly selected "insert a sterile lid speculum," while only 76% of wave 2 respondents selected his response. For the question, "What should physicians do in relation to the potential of increased intraocular pressure immediately following an Eylea injection?", 78% of wave 1 respondents correctly selected "Monitor patients after the injection procedure…," while only 62% of wave 2 respondents selected it.

10.5.3 Evaluation of key areas of concern from wave 1 survey

Prior to wave 2, Bayer revised the Eylea prescriber guide to address items that were identified as areas of key concern during review of the wave 1 survey results and redistributed the revised guide to Eylea prescribers. Physicians' knowledge on these topics was re-evaluated in the wave 2 survey and are reported below.

The use of aflibercept in women of childbearing potential

The proportion of physicians who correctly indicated that women of childbearing potential must use effective contraception during treatment and for at least 3 months after the last aflibercept injection rose slightly from 48% in wave 1 to 53% in wave 2. The proportion of physicians who reported that "Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus" was consistent across surveys (59% in wave 1 and 58% in wave 2). More than one-quarter of physicians (27% in wave 1 and 28% in wave 2) indicated that "Eylea should never be used in pregnancy," suggesting that they take a more conservative approach to aflibercept use in pregnancy. A new question was added in wave 2 to address aflibercept use in breastfeeding, to which 76% of physicians correctly reported that "Eylea is not recommended during breastfeeding."

The fact that dilation of the eye before an aflibercept injection is not necessary

Twenty-eight percent of physicians in wave 1 and 22% of physicians in wave 2 indicated that "dilate the eye" is a step that should be taken prior to marking the scleral injection site. A new question was added in wave 2 and was asked of physicians who selected "dilate the eye" to gather information on what guides physicians' decision. Among the 22% of physicians (N = 102) who selected "dilate the eye" in wave 2, the following were given as reasons:

- Eye dilation is done for regular assessment of the underlying disease or other assessments (e.g., fundus examination) (58%)

- Requirements/recommendations by national or local guidelines for intravitreal injections, local protocols, or other recommendations (54%)
- Personal preference/judgment (41%)
- Eye dilation is done in conjunction with imaging procedure(s) (26%)
- Eye dilation is not done routinely but rather upon medical judgment for each individual patient, as needed and dictated by the clinical context (25%)
- Information in the Eylea educational materials (23%)
- None of the above (3%)

Physicians' responses suggest that these physicians routinely dilate the eye to evaluate the retina prior to injection and not necessarily to prepare for the injection. In some countries, national or local guidelines (e.g., German professional societies) still recommend dilating the pupils of each patient prior to injection, which could have influenced them selecting "dilate the eye" in question 15.

The need to evaluate vision immediately after an aflibercept injection

Physicians were asked how they should evaluate a patient's vision immediately after an injection; 60% of physicians in wave 1 and 54% of physicians in wave 2 accurately responded "by hand movements or counting fingers." Approximately, one-quarter of physicians indicated that "According to the educational material, it is not necessary to evaluate a patient's vision immediately after an Eylea injection" (25% in wave 1 and 22% in wave 2).

The need to monitor patients following an aflibercept injection for elevation in intraocular pressure

Physicians were asked what they should do in relation to the potential of increased intraocular pressure immediately following an aflibercept injection. The first option, "ensure that sterile equipment is available to perform paracentesis if necessary," was selected by 65% of physicians in wave 1 and 56% in wave 2. The second option was revised in the wave 2 survey to more closely match the instructions in the prescriber guide to monitor for elevation in intraocular pressure immediately following intravitreal injection. The wave 1 response, "Undertake appropriate monitoring if increased intraocular pressure is suspected (e.g., check for perfusion of the optic nerve head or tonometry)" was correctly selected by 78% of physicians, and the wave 2 response, "Monitor patients after the injection procedure (e.g., tonometry or check for perfusion of the optic nerve head)" was correctly selected by 62% of physicians. A third option, which is a false response, was also revised slightly for the wave 2 survey. The wave 1 response, "Nothing needs to be done because increased ocular pressure is normal and never harmful" was selected by 12% of physicians; while the wave 2 response, "Nothing needs to be done because increased ocular pressure is expected" was selected by 18% of physicians.

No reuse of the same vial because of risk of infection from this multiple use

The proportion of physicians who correctly identified a false statement that the vial of Eylea is reusable between patients was high in both surveys (82% in wave 1 and 83% in wave 2). Additionally, 84% of physicians correctly reported that use of more than one injection from the vial can lead to contamination and subsequent infection (a new question added to the wave 2 survey).

10.5.4 Comparison of participants to the general population of ophthalmologists

A comparison of participants to data available for the general population of ophthalmologists was attempted in each study country. Information for the general population of ophthalmologists is very limited. However, in three of the five countries, we were able to compare participants with summary data on ophthalmologists that were publicly available. This comparison included age, sex, and practice setting variables in France, and age and sex variables in Germany and the UK. We were not able to identify characteristics of the general population of ophthalmologists in Italy or Spain.

In France, a higher proportion of survey participants worked in a hospital setting compared with the general population of ophthalmologists (69% vs. 32%). There was a higher proportion of males who completed the survey compared with the general population (79% vs. 56%, respectively), and survey participants were younger (62% vs. 33% were 49 years or younger) (8). In Germany, participants and the general population of ophthalmologists had a similar proportion that worked in an office setting (72% vs. 83%), but the survey participants included a somewhat higher proportion of males than the general population (67% vs. 51%) (9). In the UK, sex was consistent across the survey (67% male and 25% female[2]) and the general population of ophthalmologists (69% male and 31% female), but the survey participants were slightly younger (64% vs. 57% were 49 years or younger) (10).

10.6 Adverse events/adverse reactions

This study was not designed to collect information on individual adverse events or adverse drug reactions, which are better collected using other study designs. No adverse events were reported during the wave 2 survey because the survey included only closed-ended questions.

[2] The remaining 8% of physicians in the UK opted not to answer this question.

11. Discussion

11.1 Key results

In general, physicians' knowledge of questions related to aflibercept storage and preparation was high; the proportion of correct responses ranged from 83% to 92% for all four correct statements, which physicians had to identify as true. One of the four correct statements asked physicians whether use of more than one injection from the vial can lead to contamination and subsequent infection; 84% correctly identified this item as a true statement. The remaining three items in this series were incorrect statements that the physician had to identify as not true. The proportion of correct responses was as follows for identifying incorrect statements: 83% correctly identified "the vial of Eylea is reusable between patients and can be used for multiple injections" as not true; 68% correctly identified "Eylea is a suspension, which contains particulates and is cloudy" as not true; and 44% correctly identified "prior to usage, the vial of Eylea may be kept at room temperature for up to 48 hours" as not true.

Physician knowledge on dosing was high. Seventy-eight percent knew the recommended dose for aflibercept is 50 microliters (2 mg), and 82% knew that the aflibercept vial contains more than the recommended dose of aflibercept, and excess volume should be expelled before injecting. However, only 58% correctly indicated that after removing all of the drug from the aflibercept vial with a syringe, the plunger of the syringe should be depressed until the tip aligns with the 0.05 milliliters (mL) line on the syringe.

Overall, physicians' knowledge of actions to prepare patients before the start of Eylea treatment was high; correct responses ranged from 67% to 94%. Most physicians knew the contraindications for aflibercept use, with correct responses to individual items ranging from 82% for severe intraocular inflammation to 92% for known hypersensitivity to aflibercept. Fifty-eight percent of physicians correctly indicated that aflibercept should not be used in pregnancy unless the potential benefit outweighed the potential risk to the fetus; an additional 22% of physicians seemed to take a more conservative approach and indicated that aflibercept should never be used in pregnancy. Half of physicians (53%) selected the correct time frame for which women of childbearing potential must use effective contraception, and 76% correctly indicated that aflibercept is not recommended for women who are breastfeeding.

Knowledge was also high on the topic of injection procedures. Most physicians correctly responded to questions on appropriate use of topical anesthesia (89%) and disinfectant (92%). When asked to identify steps that should be taken prior to marking the scleral injection site, most physicians correctly selected "cover the eye with a sterile drape" (84%) and "insert a sterile lid speculum" (76%). Fewer than one-fourth (22%) of physicians indicated that the eye should be dilated (this was not a correct response option). In a follow-up question directed to these physicians, more than half of physicians indicated that eye dilation is done for regular assessment of the underlying disease or other assessments (58%) or based on requirements/recommendations by national or local guidelines for intravitreal injections, local protocols, or other recommendations (54%).

Fifty-four percent of physicians correctly reported that patients' vision should be evaluated immediately after an aflibercept injection by hand movements or counting fingers. Most physicians (83%) knew that an increase in intraocular pressure has been seen within 60 minutes after an aflibercept injection. Knowledge was notably lower for the two actions to take in relation to potential increased intraocular pressure: ensure that sterile equipment is available to perform paracentesis if necessary (56%) and monitor patients after the injection procedure (e.g., tonometry or check for perfusion of the optic nerve head) (62%).

Knowledge was high for the need to instruct patients to report any symptom of possible intraocular inflammation (81%) and endophthalmitis (87%). Knowledge was also generally high for recognizing the correct signs, symptoms, or diagnoses of possible side effects (ranging from 69% to 92% for individual side effects).

In general, there was noticeable variation in physicians' knowledge across countries with a few exceptions. Some differences could be explained by the variation in composition of participants within each country. For example, 70% of physicians in the UK versus 54% of physicians in Italy reported that their focus within ophthalmology was retina. Additionally, 39% of physicians in the UK versus 14% of physicians in Italy reported administering 40 or more aflibercept injections per month.

Overall, physicians' knowledge tended to be highly associated with average number of aflibercept injections performed per month. For most questions, the proportion of correct responses was higher among physicians who reported administering higher numbers of aflibercept injections. The physicians' focus within ophthalmology tended also to be highly associated with knowledge. Physicians who indicated their focus included the retina had the highest proportion of correct responses on almost all of the questions, while those whose focus was limited to general ophthalmology frequently had much lower proportions correct. The remaining physicians (who indicated their focus was in glaucoma, cataract, or other) had significantly lower knowledge than the retina physicians on almost every question.

The majority of physicians (89%) reported that they received the SmPC. Of those, 83% reported that they reviewed the document, and 81% found it helpful or extremely helpful. Likewise, most physicians (82%) reported that they received the prescriber guide. Of those, 82% of physicians reviewed the guide, and of those, 85% found it to be helpful or extremely helpful on a 4-point scale. The physicians who said they reviewed the prescriber guide were asked how long ago they reviewed it, and 66% said more than 3 months ago, 24% said between 1 week and 3 months ago, 6% said less than 1 week ago, and 5% answered "I don't know."

More than half of physicians (54%) reported that they received the intravitreal injection procedure video. Of those, 72% of physicians reviewed the video, and of those, 81% found it to be helpful or extremely helpful. Two-thirds of physicians (65%) reported that they received the indication-specific patient booklet. Of those, 70% said they reviewed it, and of those, 83% found it to be helpful or extremely helpful.

There was variation across the countries in the receipt of the educational materials. The proportions of reported receipt of the SmPC was consistently high across countries (86%-96%), while the Eylea Prescriber Guide varied from 73% in Spain to 91% in Italy. The proportion who reported receipt of the intravitreal injection procedure video varied from 46% in Spain to 60% in Germany, and the proportion of receipt of the indication-specific patient booklet including a patient information audio CD and the patient information leaflet went from 47% in Spain to 76% in the UK.

Overall, 61% of physicians reported providing the patient booklet to most or all of their patients (ranging from 48% in France to 77% in the UK).

11.2 Limitations

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 (11). 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 these physicians. Therefore, the study participants may not necessarily perfectly represent all physicians who have prescribed/administered aflibercept.

The primary source of physician recruitment was an online physician panel. Panels provide efficient access to a large number of physicians available to participate in various research and thus provide a more feasible approach to physician recruitment than some other recruitment sources/methods (e.g., sponsor lists of physicians). Per the General Data Protection Regulation in Europe, Bayer can only share with PPD general lists of ophthalmologists (as opposed to known prescribers of aflibercept) with contact information that is publicly available (often limited to physician and/or clinic name and postal address). To be able to provide PPD with more specific contact information, Bayer would need to obtain consent from physicians before releasing their personal identifying information to a third party, a process not considered practical for this type of study.

In general, physician response rates for web-based surveys have been somewhat low historically. In Germany, for post-authorization 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. This requirement may explain why the physician response to the survey was particularly lower in Germany, and despite increased efforts to recruit physicians, the target study size for Germany was not quite reached (57 of the target of 60 completed the survey).

Low response rates may result in higher likelihood that participating physicians are not representative of the target population of all prescribing physicians. Thus, the resulting estimates of physician understanding about aflibercept may be biased.

As is true with most surveys, it is possible that participants who completed the questionnaire differ from nonparticipants 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. A comparison of participants and nonparticipants in the physician assessment was not possible because physicians who do not wish to participate in the survey are likely not to respond to the invitation. However, to the extent possible, we used limited data available in the public domain to compare characteristics of the participants to what is known about the overall ophthalmologist population. The characteristics of participants in Germany and the UK were fairly similar to data found on their overall ophthalmologist populations; in France, participants were more likely to be younger, male, and hospital based. Some potentially important characteristics, such as physician focus within ophthalmology, volume of injections, years in practice, are available only from the study participants and could not be compared with the overall ophthalmologist population. Because the information available for direct comparison was limited, we also examined variables that might differ between the participant and the overall ophthalmologist population to see if they were associated with knowledge level. Those findings are included in the report.

In addition, the study 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 have Internet access, particularly physicians who are members of an online panel.

The study targeted a minimum of 300 physicians (approximately 60 to 100 physicians per country). The majority of the analysis focused on aggregated data across all countries. Although the report displays country-specific findings, there may be limitations with drawing country-specific conclusions.

Bayer distributed the revised educational materials through May 2019. Distribution of the materials was independent of the study. The survey was conducted after physicians had received the revised Eylea Prescriber Guide and 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.

11.3 Interpretation

Knowledge and behavior may be influenced by many factors, including availability and access to information, years of experience, practice setting, country-specific health care systems, literacy and numeracy, cultural differences, beliefs, and motivation.

The key content of the physician educational materials includes the importance of using the correct sterile injection technique and monitoring and managing potential injection-related adverse events. Knowledge of injection procedures, including sterile injection technique, was very high. While a small proportion of the physicians indicated that they dilate the eye before an aflibercept injection, a follow-up with these physicians suggests that more than half routinely dilate the eye to evaluate the retina for regular assessment and/or due to recommendations by national or local guidelines prior to an injection and not necessarily to prepare for the injection.

Physicians' knowledge of the potential for intraocular pressure within 60 minutes after an aflibercept injection, potential side effects, and instructions to patients was high. However, only slightly more than half of physicians responded correctly to each question regarding evaluating patients' vision after injection and steps to take in relation to the potential for increased intraocular pressure.

In general, physicians' knowledge of storage and preparation guidelines, dosing, safe use, and injection procedures was very high.

Most physicians either correctly indicated that aflibercept should not be used in pregnancy unless the potential benefit outweighed the potential risk to the fetus or seemed to take a more conservative approach and indicated that aflibercept should never be used in pregnancy. More than half of physicians selected the correct time frame for which women of childbearing potential must use effective contraception, and the majority correctly indicated that aflibercept is not recommended for women who are breastfeeding. Given the average age of aflibercept patients these are topics that are less frequently encountered.

No a priori thresholds of correct responses to the knowledge questions were specified for this study. Sponsors and regulators in the United States and Europe often find reassurance if correct responses for knowledge questions are reported by at least 80% of study participants (6,11-13). In a review of survey-based studies evaluating the effectiveness of risk-minimization measures in Europe, a threshold of at least 80% of correct responses was used to define the success of risk-minimization measures in 2 of 11 surveys registered in the EU Post-Authorization Study Register (14). In the other nine surveys, a majority of participants responding correctly was considered a successful result (14).

In reviewing each knowledge area for the current study, the proportion of correct responses was > 80% for 5 of the 7 items on storage and preparation, one of the 3 items on dosing, 5 of

the 9 items on safe use, four of the six items on injection procedure, and 5 of the 12 items on side effects.

The majority of physicians reported receipt of the SmPC and Eylea Prescriber Guide. Approximately half of physicians reported receipt of the Eylea intravitreal injection procedure video. Two-thirds of physicians reported receipt of the Patient Booklet. Reported receipt for educational materials was fairly consistent across countries. It was encouraging to see that, among physicians who reported receipt of the material, review of the material was high.

A recent publication (15) reported the results of a multinational survey of 800 European physicians that assessed the receipt of educational materials. For that study, physician-reported receipt of the educational materials ranged from 16% to 69% across the participating countries.

The overall response rate for the survey was 9.6% (compared with 5.1% in wave 1). Response rates for physician surveys are traditionally low, and the response rate for this study is somewhat artificial because responses were not allowed once quotas for responders were met; thus the true response rate, although unmeasurable, would be higher. Comparing response rates in this survey with that of other, similar studies is challenging due to high variability in the way participation is reported and use of different terminologies and indicators to measure participation (16). However, multiple physician surveys evaluating risk-minimization measures in the United States and Europe have shown response rates below 10% (17-19). A variety of methodological factors may account for the low response rates to survey studies (e.g., method of contact, mode of survey administration, use of incentives) in addition to physician-related factors (e.g., the lack of time, lack of interest in the survey topic, concerns about confidentiality, and office policies) (20).

A comparison of participant characteristics to the available data on the overall ophthalmologist population within each country revealed that participants from Germany and the UK were similar to the overall ophthalmologist population within those respective countries, but some differences were identified in France. To address any concern about representativeness, particularly in France and in the countries where we did not have data on the overall ophthalmologist population to compare with study participants, we stratified the study results by sex, age, and practice setting to see if these factors were associated with knowledge and thus, if an imbalance between study participants and the overall population, could lead to bias. The associations between these variables and participant knowledge was mixed. Participants' sex was not associated with knowledge levels; the proportion of correct responses for males and females were within 10% of each other on almost every question. In general, participants who indicated that they were hospital based had slightly higher knowledge than office-based physicians. There was no clear pattern in the association between participants' age and knowledge levels; although participants who were younger than 40 years old or 60 years or older had somewhat higher knowledge than other age categories. As the pattern was not consistent across age, we suspect the observed association may be spurious results arising from sampling variability. Taking the general similarities between the study participants and the country-specific ophthalmologist populations in the measured characteristics in combination with the knowledge results stratified by these characteristics, we do not think that there is large potential for bias in our overall results.

Across many of the knowledge questions, the proportion of correct responses was slightly lower on wave 2 than wave 1. One factor driving this could be that there was a somewhat lower proportion of physicians who indicated "retina specialist" as being their focus within ophthalmology in wave 2 compared with wave 1 (63% versus 74%). When examining the wave 2 results stratified by focus within ophthalmology, we found that those physicians with

a focus on the retina had higher proportions of correct responses than the other categories of focus. Thus, having fewer physicians who focused on the retina in wave 2 of the survey may have led to the trend in slightly lower knowledge overall.

11.4 Generalizability

As noted in Section 10.2, the study achieved great diversity in physician characteristics within the five countries, allowing for stratification of results by those characteristics. We saw heterogeneity of some results by country; it is unknown how well these results would relate to other countries.

12. Other information

Not applicable.

13. Conclusion

The study successfully evaluated whether physicians received the educational materials for aflibercept and assessed physician knowledge and understanding of key safety information, as well as the use of the materials. Physicians' reported receipt of the SmPC and prescriber guide was high (89% and 82%, respectively). The relatively high level of knowledge among physicians also suggests that the key safety information is available to the treating physicians.

Physicians' knowledge of the most important topics outlined in the educational materials was high. For example, knowledge on possible side effects ranged from 69% to 92%.

In general, the observed patterns of knowledge among the physicians are as expected—with greatest knowledge on the most important risks emphasized in the educational material and SmPC and lower knowledge on topics that are less frequently encountered and for which we would assume that physicians would consult the label and/or prescriber guide rather than relying on their memory (e.g., use in women of childbearing potential).

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Appendices

Annex 1. List of stand-alone documents

Annex 2. Physician questionnaire

Annex 3. Results tables, overall and by country

Annex 4. Results tables, by other stratifications

Annex 5. Graphical comparison of wave 1 and 2

Annex 6. Signature pages

Annex 1: List of stand-alone documents

Table 1-1. List of stand-alone documents

Document name	Final version and date (if available)
Eylea Prescriber Guide	12 JUN 2018
Statistical Analysis Plan	V 1.0, 22 OCT 2018

Annex 2: Physician questionnaire

Annex 3: Results tables, overall and by country

Annex 4: Results tables, by other stratifications

Annex 5: Graphical comparison of wave 1 and 2

Annex 6: Signature pages

Signature Page

Title	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey
Report version and date	v 1.0 21 AUG 2020
Study type/study phase	☒ <PASS> Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS 30727
Medicinal product	Eylea (aflibercept)
Product Reference	EU/1/12/797/001 and EU/1/12/797/002
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD (OS conduct responsible at Bayer)

Date, Signature:

_____, PPD _____

Signature Page

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PPD

1/ Sept./2020

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