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

Acronym/Title	APOLLON — A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept
Report version and date	Version 1.0– 03 JUL 2018 – Interim report 6 months follow-up
Study type / Study phase	PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	EUPAS15687
Active substance	Ophthalmological / Anti-neovascularization agents (S01LA05), Aflibercept, BAY-86-5321
Medicinal product	EYLEA®
Product reference	VIAL: EU/1/12/797/002
Procedure number	Not applicable
Study Initiator and Funder	Bayer Healthcare SAS, 59120 Loos, France
Research question and objectives	The main objectives of this observational study were to describe outcomes, monitoring and treatment patterns in patients with DME in routine clinical practice who were either treatment naïve patients or previously treated patients. The total study population has been evaluated as well as the 2 subgroups (previously treated patients and treatment naïve patients). This study was designated to answer HAS requirements.
Country(-ies) of study	France

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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	Moncef Boukerrou, Country Medical Director

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1. Abstract

Acronym/Title	APOLLON – A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept.
Report version and date **Author**	Version 1.0 – 03 JUL 2018 – Interim report 6 months follow-up Ingrid DUFOUR
Keywords	Diabetic macular edema, vascular endothelial growth factor, intravitreal aflibercept, visual acuity.
Rationale and background	Macular edema is the most common cause of vision loss in patients with diabetic retinopathy. Although focal/grid laser has been the standard of care for DME, the role of VEGF in the pathogenesis of DME has led to investigation of anti-VEGF agents in these patients. Ranibizumab has been evaluated in key clinical studies such as RESOLVE, RESTORE, RISE and RIDE. In these trials, the anti-VEGF treatment ranibizumab offered substantial visual and anatomical benefits in patients with DME. These benefits were maintained for 3 years with regular monthly dosing, and for 5 years with less frequent dosing in RIDE and RISE results. Safety evaluation was generally similar across the ranibizumab and sham groups. However in RISE and RIDE an imbalance in AE's between the 0.3 and 0.5mg ranibizumab treatment groups led the study sponsor to only submit the 0.3mg dose for approval at the FDA. The benefits of IVT aflibercept in DME have been established in three key studies, DA VINCI, VIVID^{DME} and VISTA^{DME}. At week (W) 52, W100 and W148, intravitreal injection of aflibercept demonstrated significant superiority in functional (mean BCVA gains) and anatomic endpoints (CRT reduction) over laser, and was well-tolerated.

	Recently the Diabetic Retinopathy Clinical Research Network (DRCRnet) conducted the study Protocol T, in order to evaluate safety and efficacy of IVT aflibercept, bevacizumab, and ranibizumab in the treatment of diabetic macular edema. The Protocol T study showed in DME statistically significant superior improvement in mean VA for 2 mg IVT aflibercept compared to 0.3 mg ranibizumab and 1.25 mg off label bevacizumab while patients have required 9 IVT aflibercept, 10 IVT ranibizumab or 10 IVT bevacizumab (p-values respectively aflibercept-bevacizumab : p=0.045, aflibercept - ranibizumab: p=0.19, bevacizumab–ranibizumab: p=0.2). In the group of patients with moderate visual impairment (baseline vision worse than 20/40), IVT aflibercept demonstrated clinically meaningful and statistically significant VA improvements. In patients with worse initial baseline VA, improvement in VA of at least 15 letters, (3 Snellen lines) was observed in 67% of aflibercept-treated eyes and 41% of bevacizumab-treated eyes (a relative gain of 63%) and in 50% of ranibizumab-treated eyes (a relative gain of 34%). These VA results were supported by the anatomical finding that IVT aflibercept reduced central retinal thickness more than ranibizumab. All three treatments were well tolerated without significant differences between groups. IVT aflibercept was approved for use in DME by the EMA and FDA in 2014. According to the Summary of Product Characteristics, IVT aflibercept is recommended to be injected monthly for five consecutive months, which constitutes the loading dose. The loading dose is followed by one injection every two months. After 12 months of treatment, the interval between two injections can be prolonged or adapted according to visual and anatomical results. HAS (Haute Autorité de Santé) requires the MAH to assess the use of IVT aflibercept in routine clinical practice. In particular, specific requests include the description of the treated population, the conditions of use of the product, the reasons for discontinuation of treatment and the evaluation of long-term effectiveness and safety. In response to the HAS requirements, it was decided to conduct a prospective observational cohort study to describe the use of IVT aflibercept in treatment naïve and previously treated patients with DME .
Research question and objectives	The main objectives of this observational study are to describe outcomes, monitoring and treatment patterns in patients with DME in routine clinical practice who are either treatment naïve patients or previously treated. The total study population has

	been evaluated as well as the 2 subgroups (previously treated patients and treatment naïve patients). This study was designated to answer HAS requirements. The primary objective of the study was to describe the mean change in Best-Corrected Visual Acuity (BCVA) from baseline through 12-month follow up. The secondary objectives were: ▪ To describe baseline characteristics of DME patients initiating IVT aflibercept in routine clinical practice: demographics and clinical characteristics including BMI, duration of diabetes, HbA1c level and blood pressure ▪ To describe anatomical and functional changes (BCVA, CRT, presence of fluid) from baseline through 12-month follow up ▪ To describe anatomical and functional changes from baseline through 24-month follow up ▪ To describe change in FA/FP evaluations between baseline and 24-month follow-up ▪ To describe the evolution of HbA1c level and blood pressure throughout 24 months ▪ To describe DME monitoring in patients receiving IVT aflibercept routine clinical practice ▪ To describe the regimen with IVT aflibercept from initial visit to 24-month follow-up visit ▪ To describe the frequency and severity of ocular and non-ocular adverse events. ▪ To describe type and duration of previous treatments for DME in previously treated patients.
Study design	This study is a prospective, non-controlled, multi-center, observational study conducted in ophthalmological clinics and practices throughout France. The decision upon starting IVT aflibercept was made at the discretion of the attending physician, according to his/her medical practice. The data were collected for each consecutive patient in whom a treatment with IVT aflibercept is initiated between Q3 2016 and Q3 2017. Patients should be followed up for 24 months or until it is no longer feasible (e.g. lost to follow-up, withdrawal, death, and transfer to another physician), whichever is earlier.
Setting	The study planned to involve 60 ophthalmology centers specialized for retina (retinologists) (clinics and hospitals, private and public). Physician recruitment was made from a

	national database of relevant professionals from the OneKey file CEGEDIM. The participating centers had to include all patients who met eligibility criteria (i.e. patients with VA loss due to DME [in accordance with the local SmPC and HAS recommendation] and initiating treatment with IVT aflibercept) in a consecutive way until 400 patients were enrolled. The decision to prescribe the medication was separated from the decision to include the patient in the study. The study population consisted of patients with VA loss due to DME (in accordance with the local SmPC and HAS recommendation), who had never been treated with aflibercept, and initiating treatment with IVT aflibercept per the ophthalmologist ‘s discretion. The study protocol did not define a schedule for the visits. Follow-up visits occurred during routine practice and were scheduled at the discretion of the treating ophthalmologist. All patient-based data required for the purposes of this study were collected, at least, at the initial visit, after each IVT injection during the first five months, at 6, 12 and 24 months after the first injection of IVT aflibercept.
Subjects and study size, including dropouts	The Diabetic Retinopathy Clinical Research Network recently reported a comparison of IVT aflibercept, ranibizumab, and bevacizumab in patients with diabetic macular edema. In the IVT aflibercept group the mean visual acuity improved of 13+/-11 letters. A sample size of 385 produces a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 1,099 when the known standard deviation is 11,000. The target was to enroll 400 patients in total. The participating centers had to include all patients who meet eligibility criteria in a consecutive way until 400 patients were enrolled.
Variables and data sources	The primary variable in this study was the change in BCVA from initial visit to 12 months (Mo) follow up. Secondary variables were: ▪ Mean change in BCVA between baseline and 24 Mo ▪ Mean change in CRT between baseline and 12 Mo ▪ Mean change in CRT between baseline and 24 Mo ▪ Proportion of patients with no fluid determined by OCT at baseline, 12 Mo and 24 Mo

	▪ Proportion of patients with presence of any of these parameters at baseline and 24 Mo (according to FA or FP assessments) o Micro-aneurysms and haemorrhages o Neovascularization of the disc o New vessels elsewhere than the disc o capillary leakage o Area of fluorescein leakage due to new vessels o Hard exudates o Soft exudates (cotton wool patches) o Micro-aneurysms and haemorrhages o Intra retinal micro vascular abnormalities o Neovascularization of the disc o New vessels ▪ Change in HbA1c level and blood pressure during the 24-month follow-up period ▪ DME monitoring: o History of DME monitoring o No. of monitoring visits without injection (e.g diagnostic purposes, monitoring of adverse events / safety) over 12 and 24-month periods o No. of visits combining monitoring and injection over 12 and 24-month periods o No. of monitoring visits for diabetes (by diabetologists, general practitioners) outside the study centre over 12 and 24-month periods (if known by the ophthalmologist) o No. of OCT assessments over 12 and 24-month follow-up periods o No. of FP assessments over 12 and 24-month follow-up periods o No. of FA assessments over 12 and 24-month follow-up periods o No. of VA measurements over 12 and 24-month follow-up periods ▪ IVT aflibercept regimen o Reason for initiating IVT aflibercept (based on VA, OCT, both, other) o Proportion of patients with bilateral treatment o No. of treatment / injection visit over 12 and 24-month follow-up periods o Mean, minimal and maximum interval (days) between injections o Type and frequency of adjunctive therapy post IVT aflibercept initiation (ie, surgery, focal laser, steroids, etc.)

	▪ Frequency and severity of ocular and non-ocular adverse events ▪ Type, duration (months) of the previous treatment(s) and date of the last administered DME treatment, in previously treated patients. Except for previous treatment(s), all parameters were described in the overall population, in treatment-naïve patients and in previously treated patients.
Results	From 15 SEP 2016 to 05 JUL 2017, 61 ophthalmologists participated in the study and contributed 402 patients, 364 (90.5%) of whom are included in the FAS. At the time of the data cut-off of the interim analysis (19 FEB 2018), 283 patients (146 treatment naïve patients and 137 previously treated patients) met criteria to be included in the FAS and had been followed at least 6 months within the study. Results presented in this interim OS report refer to these 283 patients. Patients had mean (±SD) age of 65.6 ± 11.3 years (range, 19-90 years) and were slightly more male (54.8%). Less than 10% of patients were current smokers and 30.8% were former smokers. Mean (±SD) body mass index was 29.6 ± 6.1 kg/m² and mean (±SD) blood pressure was 141 ± 19 / 77 ± 11 mmHg. Globally, demographic data did not significantly differ between treatment naïve and previously treated patients. Mean (±SD) time since diabetes diagnosis was 18.0 ± 12.6 years for treatment naïve patients and 19.2 ± 10.8 years for previously treated patients. Mean (±SD) glycemia was 14.2 ± 17.4 mmol/L in treatment naïve patients compared to 8.8 ± 8.9 mmol/L in previously treated patients. Mean (±SD) HbA1c level was 7.7 ± 1.3%. Mean (±SD) time since DME diagnosis for study eye was 7.6 ± 19.5 months in treatment naïve patients and 37.6 ± 36.6 in previously treated patients. Median time were 1.0 month and 24.9 months, respectively. Among previously treated patients, 88 (67.2%) patients had been previously treated with IVT anti-VEGF (mainly with Lucentis [84 patients], 84 (64.1%) patients had been previously treated with laser (mainly pan-photocoagulation laser [58 patients]) and 32 (24.6%) patients had been previously injected with intraocular steroids. Baseline BCVA and OCT assessments (CRT and presence of retinal fluid) were similar in treatment naïve patients and previously treated patients. Mean (±SD) baseline BCVA was 60.7 ± 15.5 letters with 59.0% of patients presenting with a

	BCVA ≤65 letters, and mean CRT was 449.4 ± 129.9 µm with 77.4% of patients presenting with a CRT ≥ 350 µm. Almost all patients (95.8%) had intra-retinal fluid visible on OCT and 28.6% had sub-retinal fluid visible. The only significant difference between the 2 cohorts concerns history of cataract surgery that was more frequent in previously treated patients (45.1% vs. 25.9% in treatment naïve patients). Mean (±SD) number of injections received per patient during the first 6-month follow-up period was 5.3 ± 1.2 injections in treatment naïve patients and 4.8 ± 1.3 injections in previously treated patients. Median number of injections was 5 in both cohorts. Overall, 41.7% of patients received the loading dose (i.e. 5 consecutive monthly injections, according to the SmPC) but 72.8% received at least 5 injections during the first 6-month follow-up period. Fifteen (5.3%) patients discontinued EYLEA® permanently, mainly to switch to another treatment (9 patients). A large majority of patients (86.2%) received at least one concomitant medication during the 6 months follow-up, mainly non ophthalmological medications (82.0%). Less than one quarter of patients (20.9%) received a concomitant ophthalmological medication, mainly sympathomimetics in glaucoma therapy (5.0%), antiinfectives (4.2%) and beta blocking agents (3.9%). Overall 20 (7.1%) patients experienced at least one concomitant ophthalmological surgery within the first 6 months of follow-up, mainly cataract surgery (12 patients) and 46 (16.3%) patients have received at least one adjunctive therapy during the first 6 months follow-up, mainly laser therapy (37 patients). Mean (±SD) change in BCVA at 6 months was 8.5 ± 11.9 letters in treatment naïve patients vs. 6.4 ± 13.4 letters in previously treated patients. Median change were respectively +8.0 and +4.0 letters. More than half of patients (54.8%) achieved an improvement in BCVA of at least 5 letters (1 line) 6 months after the first injection of IVT aflibercept, with 35.0% achieving a gain of at least 2 lines, and 22.3% achieving a gain of at least 3 lines. Very few patients (3.9%; 11 patients) lost more than 2 lines and most of them (8 patients) were previously treated patients. At baseline, respectively 30.8% and 19.7% of treatment naïve and previously treated patients had a BCVA ≥70 letters. At 6 months, percentages reached 67.8% in treatment naïve patients and 30.7% in previously treated patients. Overall, the rate of patients achieving BCVA ≥70

	letters increased by 24.4% 6 months after the first injection of IVT aflibercept. Mean (±SD) CRT at baseline was 449 ± 130 µm and was similar in treatment naïve and previously treated patients. Mean (±SD) change in CRT at 6 months was 109 ± 135 µm. No difference in CRT change was observed in mean change between the 2 subgroups. Median change were respectively -84 and -81 µm in treatment naïve and previously treated patients. Sixty-six patients (17.1%) experienced at least one ophthalmological TEAE possibly related to EYLEA® treatment, but none of them was serious. Twenty-eight patients (7.3%) experienced at least one ophthalmological TEAE related to procedure, including one serious TEAE. For 5 patients, non-serious ophthalmological TEAE led to EYLEA® withdrawal. Overall, 124 patients (32.1%) experienced 282 non-ophthalmological TEAE, 32 (8.3%) of whom having experienced a serious non-ophthalmological TEAE. Sixty-six patients experienced at least one non-ophthalmological TEAE possibly related to EYLEA® treatment, and TEAE was serious in 2 of them (hemorrhagic stroke and coronary artery stenosis). Three patients experienced fatal TEAE (myocardial infarction, cardiac decompensation and cardiogenic shock), but none of them was assessed as related to EYLEA® treatment.
Discussion	283 patients were analyzed through this interim analysis at 6 months, 137 of whom were previously treated patients (i.e. patients previously treated with an anti-VEGF agent, or intra-ocular steroids for their OMD or previously treated with laser in the study eye for their OMD) and the 146 remaining were treatment naive patients. Patients had mean (±SD) age of 65.6 ± 11.3 years (range, 19-90 years) and most of them were followed for their diabetes for more than 10 years. Median time since DME diagnosis was 1 month in treatment naïve patients vs. 25 months in previously treated patients. Approximately two third of previously treated patients had been previously treated with IVT anti-VEGF (other than aflibercept) which is in accordance with the standards of use. Baseline BCVA and CRT were similar in treatment naïve patients and previously treated patients. Mean (±SD) baseline BCVA was 60.7 ± 15.5 letters, and mean CRT was 449 ± 130 µm. Over the 6-month follow-up period, patients had a mean (±SD) of 6.9 ± 1.4 visits referring to study eye during which they received a mean (±SD) of 5.3 ± 1.2 injections.

	The evolution of BCVA and CRT at 6 months indicate an improvement of visual and anatomic characteristics in both subgroups (treatment naïve and previously treated patients), but improvement in BCVA was more important in treatment naïve patients (median change of +8.0 vs. +4.0 letters in previously treated patients). This important improvement in treatment naïve patients is also illustrated by the proportion of patients who achieved the patient beneficial threshold of 70 letters for BCVA assessment which increased by 37% at 6 months compared to 11% in previously treated patients. As regards CRT results, treatment naïve patients and patients previously treated had similar CRT before the first injection of EYLEA® (i.e. 449.4 ± 129.9 µm) which suggest that previous DME treatment did not significantly improve anatomic parameters while EYLEA® treatment significantly reduced edema in both subgroups (CRT decreased by -108.5 ± 134.6) after 6 months of treatment. These results are promising but long-term efficacy of IVT aflibercept must be confirmed at 12 and 24 months. Safety results are common to the known safety profile observed in RCT. No new safety event has been identified in this analysis. Among the population, 66 (17.1%) patients experienced adverse event related to EYLEA®, and only 2 patients a serious one. This first interim analysis of patients treated with IVT aflibercept in real world condition is promising. Treatment with IVT aflibercept resulted in BCVA improvement at 6 months with a mean gain of 8.5 letters for treatment naïve and 6.4 letters for previously treated patients, respectively. Macular edema was also reduced in both subgroups (CRT decrease by 107 µm and 110 µm respectively in treatment naïve and previously treatment patients). No new safety profile has been observed EYLEA® with 17.1% of patients having experienced an EYLEA® related adverse event and 0.5% (2 patients) having experienced a serious EYLEA® related adverse event.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document (see Table 23: List of stand-alone documents, Annex 1 which is available upon request.

2. List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (Classification System)
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Central Retinal Thickness
DM/DR	Diabetic Macula/Diabetic Retinopathy
DME	Diabetic Macular Edema
DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicine Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HbA1c	Glycated haemoglobin A1c
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRMA	Intra-Retinal Micro vascular Abnormalities
IVT	Intravitreal
LOCF	Last Observation Carried Forward
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
Mo	Month
N/A	Not Applicable
No.	Number
OCT	Optical Coherence Tomography
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PT	Preferred Term
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class

VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO DD	World Health Organization Drug Dictionary

3. Investigators

Contact details on the coordinating and / or principal investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Table 23: List of stand-alone documents, Annex 1) which is available upon request.

Administrative changes of responsible persons have been documented by updating the respective lists, but do not require formal protocol amendments.

4. Other responsible parties

Information on the Steering Committee Members is kept as stand-alone document (see Table 23: List of stand-alone documents, Annex 1 and also the respective Charters) and is available upon request.

Administrative changes of responsible persons and / or the composition of the committees have been documented by updating the respective lists, but do not require formal protocol amendments.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	21 SEP 2016	21 SEP 2016	
End of data collection	21 OCT 2019	Not applicable	Interim analysis
Registration in the EU PAS register	15 DEC 2015	13 JAN 2017	Update of EU PAS register number
IEC or IRB approval - Study protocol version 1.0		First approval: 13 JAN 2016 Last approval: 18 JUL 2016	
IEC or IRB approval -Study protocol version 2.0			No approval required, just for information.
Interim analysis 6Mo	21 SEP 2017	22 DEC 2017	Cut-off
Database Clean for Interim Analysis 6Mo		13 FEB 2018	2nd database lock
Final report of study results for Interim Analysis 6Mo		03 JUL 2018	

A complete list of IEC or IRB approvals is provided as a stand-alone document (see Table 23: List of stand-alone documents, Annex 1) which is available upon request.

6. Rationale and background

Diabetic macular edema (DME) is a complex and multifactorial disease. The Diabetes Control and Complications Trial, a study to investigate conventional versus intensive insulin therapy, reported that 27% of type 1 diabetic subjects developed DME within 9 years of the onset of diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported that the prevalence of DME in type 2 diabetic subjects increases from 3% within 5 years of diagnosis to 28% after 20 years duration.

Macular edema is the most common cause of vision loss in patients with diabetic retinopathy [1]. Although focal/grid laser has been the standard of care for DME, the role of VEGF in the pathogenesis of DME has led to investigation of anti-VEGF agents in these patients [2].

Ranibizumab has been evaluated in key clinical studies such as RESOLVE, RESTORE, RISE and RIDE. In these trials, the anti-VEGF treatment ranibizumab offered substantial visual and anatomical benefits in patients with DME. These benefits were maintained for 3 years with regular monthly dosing, and for 5 years with less frequent dosing in RIDE and RISE results. Safety evaluation was generally similar across the ranibizumab and sham groups. However in RISE and RIDE an imbalance in adverse events between the 0.3 and 0.5mg ranibizumab treatment groups led the study sponsor to only submit the 0.3mg dose for approval at the FDA. The benefits of IVT aflibercept in DME have been established in three key studies, DA VINCI, VIVID^{DME} and VISTA^{DME} [3, 4]). VIVID^{DME} and VISTA^{DME} were two similarly designed double-blinded, randomized, Phase III studies in which 872 patients with DME received either IVT aflibercept 2 mg every 4 weeks (2q4), IVT aflibercept 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation. At week (W) 52, W100 and W148, IVT aflibercept (both regimens) demonstrated significant superiority in functional (mean BCVA gains) and anatomical endpoints (CRT reduction) over laser, and was well-tolerated [4, 5].

Recently the Diabetic Retinopathy Clinical Research Network (DRCRnet) conducted the study Protocol T [6], in order to evaluate safety and efficacy of IVT aflibercept, bevacizumab, and ranibizumab in the treatment of diabetic macular edema. The Protocol T study showed in DME statistically significant superior improvement in mean visual acuity (VA) for 2 mg IVT aflibercept compared to 0.3 mg ranibizumab and 1.25 mg off label bevacizumab while patients have required 9 IVT aflibercept ,10 IVT ranibizumab or 10 IVT bevacizumab (p-values respectively aflibercept-bevacizumab: p=0.045, aflibercept-ranibizumab: p=0.19,bevacizumab ranibizumab: p=0.2). In the group of patients with moderate visual impairment (baseline vision worse than 20/40), IVT aflibercept demonstrated clinically meaningful and statistically significant VA improvements. In patients with worse initial VA, improvement d VA of at least 15 letters, (3 Snellen lines) was observed in 67% of aflibercept-treated eyes and 41% of bevacizumab-treated eyes (a relative gain of 63%)and in 50% of ranibizumab treated eyes (a relative gain of 34%) At the 1-year visit, the central subfield thickness decreased, on average, by 169±138 μm with IVT aflibercept, 101±121 μm with bevacizumab, and 147±134 μm with ranibizumab. The thickness was less than 250 μm in 135 of 205 eyes (66%),74 of 203 eyes (36%), and 116 of 201 eyes (58%), respectively. The relative treatment effect on central subfield thickness varied according to initial visual acuity ($p<0.001$ for interaction). In the group of patients with moderate visual impairment (baseline vision worse than 20/40), IVT aflibercept demonstrated clinically meaningful and statistically significant VA improvements of one line over ranibizumab with 34% more IVT aflibercept patients gaining 3 lines of vision. These VA results were supported by the anatomical finding that IVT aflibercept reduced central retinal thickness greater than

ranibizumab; however this difference was not significant. All three treatments were well tolerated without significant differences between groups.

IVT aflibercept was approved for use in DME by the EMA and FDA in 2014. According to Summary of Product Characteristics, IVT aflibercept is recommended to be injected monthly for five consecutive months, which constitutes the loading dose. This loading dose is followed by one injection every two months. After 12 months of treatment, interval between two injections can be prolonged or adapted regarding visual and anatomical results. According to HAS (French Health Authority) recommendation, only patients with a baseline VA less or equal to 5/10 (≤20/40) are eligible to anti-VEGF treatment. Moreover, HAS required from the MAH some additional analyses to assess the use of IVT aflibercept in routine clinical practice. In particular, specific requests included description of the treated population, the conditions of use of the product, the reasons for discontinuation of treatment and the evaluation of long-term effectiveness and safety. In response to the HAS requirements, it was decided to conduct a prospective observational single and cohort study to evaluate the use of IVT aflibercept on patients with DME in the routine clinical practice in France.

The APOLLON Study is the first observational study conducted in France in treatment naïve and previously treated DME patients starting IVT aflibercept. The primary objective of this study was to assess the effectiveness of IVT aflibercept in this patient population in routine clinical practice.

7. Research question and objectives

The main objectives of this observational study were to describe outcomes, monitoring and treatment patterns of patients with DME either treatment naïve patients or previously treated patients. This study has been conducted in France in routine clinical practice. The total study population was evaluated as well as the 2 subgroups (previously treated patients and treatment naïve patients).

7.1 Primary objective

The primary objective of this study was to describe the mean change in Best Corrected Visual Acuity (BCVA) from baseline through 12-month follow up.

7.2 Secondary objective(s)

The secondary objectives in this study were:

- To describe baseline characteristics of DME patients initiating IVT aflibercept in routine clinical practice: demographics and clinical characteristics including BMI, duration of diabetes, HbA1c level and blood pressure.
- To describe anatomical and functional changes from baseline through 12-month follow up
  - Mean change in central retinal thickness (CRT)
  - Proportion of patients without fluid as measured on Optical Coherence Tomography (OCT)
- To describe anatomical and functional changes from baseline through 24-month follow up
  - Mean change in BCVA
  - Mean change in CRT
  - Proportion of patients without fluid as measured on OCT
  - Proportion of patients with change in Fluorescein Angiography (FA) and Fundus Photography (FP) parameters
- To describe the evolution of HbA1c level and blood pressure throughout 24 months (when observed)
- To describe DME monitoring in patients receiving IVT aflibercept routine clinical practice

- To describe the regimen with IVT aflibercept from initial visit to 24-month follow-up visit
  - Frequency of injections over 12 and 24 months
  - Reasons for retreatment (based on VA, OCT, or other findings)
  - Type and frequency of adjunctive therapy used for the DME (e.g surgery, focal laser, steroids)
- To describe the frequency and severity of ocular and non-ocular adverse events.
- To describe type and duration of previous treatments for DME (in previously treated patients only)

8. Amendments and updates

This protocol was amended 13 JAN 2017.

A succinct list of changes made to the protocol is presented in Table 2.

Table 2: Amendments

13 JAN 2017 – V2.0	Page 1	Update of EU PAS register number
13 JAN 2017 – V2.0	Page 1	Change of study initiator and funder: Bayer Healthcare AG is replaced by Bayer Healthcare SAS
13 JAN 2017 – V2.0	Pages 7-8	Update of Responsible Parties
13 JAN 2017 – V2.0	Page 16	Update of milestones of the study
13 JAN 2017 – V2.0	Pages 1, 11, 18	Change of wording in main objectives: Replacement of effectiveness by outcomes.
13 JAN 2017 – V2.0	Pages 15, 22	Precision of the definition of study populations (description of previous treatment)
13 JAN 2017 – V2.0	Pages 11-12, 19-20	Change in study objectives: Primary objective: Change in BCVA from initial visit through 12-month follow-up is replaced by Mean change in BCVA from baseline through 12-month follow-up period. Secondary objectives: All objectives will describe a mean change instead of a change between baseline and follow up visit instead of initial visit and follow-up visit. Disappearance of fluid on Optical Coherence Tomography (OCT) is replaced by Proportion of patients without fluid as measured on Optical Coherence Tomography (OCT) at baseline, at month 12 and at month 24 To describe previous treatments for DME is replaced by To describe type and duration of previous treatments for DME

13 JAN 2017 – V2.0	Pages 13-14, 20-21, 29-30, 36	Changes to the definition of study endpoints and variables to correlate with modifications in primary and secondary objectives.
13 JAN 2017 – V2.0	Whole protocol	Change of wording in the whole protocol: "starting IVT aflibercept" is replaced by "initiating IVT aflibercept"
13 JAN 2017 – V2.0	Page 22	Eligibility: precision concerning patient receiving bilateral treatment, eye with the worst visual acuity at baseline will be considered as study eye.
13 JAN 2017 – V2.0	Page 22	Inclusion criteria Man and woman aged 18 years or more is replaced by Male or female aged 18 years or older Patient diagnosed with a visual impairment due to DME (as defined by HAS recommendation: baseline VA less or equal to 5/10) is replaced by Patient diagnosed with a visual impairment due to DME (as defined by HAS recommendation)
13 JAN 2017 – V2.0	Pages 25, 26, 27	Modification of anatomical parameters with technique of imagery: Hard exudates and soft exudates (cotton wool patches) are measured by Fundus photography instead of Fluorescein Angiography.
13 JAN 2017 – V2.0	Page 27	Precision on reason for end of observation concerning switch of IVT aflibercept treatment to another type of treatment
13 JAN 2017 – V2.0	Page 33	In imaging system paragraph, deletion of centralized central reading which will not be performed in the protocol.

9. Research methods

9.1 Study design

This study was a prospective, multi-center, observational study. The study was conducted in ophthalmological clinics and practices throughout France. It was planned to collect valid documentation on IVT aflibercept for DME in about 400 patients. The decision upon starting IVT aflibercept was made at the discretion of the attending physician, according to his/her medical practice.

The overall objectives of the study were:

- To describe the treatment and follow up of patients with DME starting IVT aflibercept in routine clinical practice (overall and in subgroups of previously treated patients and treatment naïve patients)
- To determine how disease activity is monitored in routine clinical practice during treatment with IVT aflibercept (mean number of visits, HbA1c level monitoring, blood pressure monitoring)

- To describe aflibercept regimen used in routine clinical practice (including time and number of injections, and adjunctive treatments)

This can only be accomplished in an observational study, where all decisions in terms of diagnostic procedures, treatments, and management of the disease are fully dependent on mutual agreement between the patient and the attending investigator, without interference by a sponsor or a study protocol.

The data were collected for each consecutive patient in whom a treatment with IVT aflibercept was initiated between Q3 2016 and Q3 2017. Patients have been followed up for 24 months or until it was no longer be feasible (e.g. lost to follow-up, withdrawal, death, and transfer to another physician), whichever was earlier.

9.1.1 Primary endpoint(s)

The primary endpoint in this study was mean change of BCVA from baseline to 12-month follow-up visit.

9.1.2 Secondary endpoint(s)

The secondary endpoints were:

- Mean change in BCVA between baseline and 24-month follow-up
- Mean change in CRT between baseline and 12-month follow-up and between baseline and 24-month follow-up
- Proportion of patients with no fluid determined by OCT at baseline, 12-month and 24-month follow-up
- Proportion of patients with change in FA and FP between baseline and 24-month follow-up
- Mean change in HbA1c level and blood pressure during the 24-months
- DME monitoring:
    - No. of monitoring only visits (e.g diagnostic purposes, monitoring of adverse events / safety) over 12 and 24-month follow-up periods
    - No. of visits combining monitoring and injection over 12 and 24 months.
    - No. of monitoring visits for diabetes (by diabetologists, general practitioners) outside the study centre over 12 and 24-month follow-up periods (if known by the ophthalmologist).
    - No. of OCT assessments over 12 and 24-month follow-up periods
    - No. of FP assessments over 12 and 24-month follow-up periods
    - No. of FA assessments over 12 and 24-month follow-up periods
    - No. of VA measurements over 12 and 24-month follow-up periods
- IVT aflibercept regimen
    - Reason for starting IVT aflibercept (based on VA, OCT, both, other)
    - Proportion of patients with bilateral treatment
    - No. of treatment / injection visits over 12 and 24-month follow-up periods
    - Mean, minimal and maximum interval (days) between injections
    - Type and frequency of adjunctive therapy post IVT aflibercept initiation (ie, surgery, focal laser, steroids, etc)
- Frequency and severity of ocular and non-ocular adverse events

- Type, duration (months) of the previous DME treatment(s) and date of the last administered DME treatment (in previously treated patients only)

9.1.3 Strengths and weaknesses of study design

The main objectives of this observational study were to describe effectiveness, monitoring and treatment patterns of patients with DME either in treatment naïve patients or in previously treated patients. This study was conducted in France in routine clinical practice. The total study population was evaluated as well as the 2 subgroups (previously treated patients and treatment naïve patients). All data required for this study were collected during routine clinic visits. Any decisions on diagnostic- and treatment-related procedures were made at the discretion of the attending ophthalmologist according to his/her medical practice.

An observational design addressed the objectives of this study. Since the decision of starting IVT aflibercept was taken independently of the study, data will give interesting insights on the characteristics of patients with DME, and on conditions of use of IVT aflibercept. The potential weakness of the study was that some data could be missing since data were collected during routine visits and ophthalmologists do not perform all examinations at each visit. The imputation of missing data may, however, partially solve this issue. In order to reduce the number of missing data, monitoring and quality reviews have been performed during the study.

Data collection occurred as patients were enrolled into the study (prospective enrollment). The prospective approach usually provides good level of data quality, as data are more complete and the validity is often easy to verify.

Prospective data may suffer from biases (e.g. interviewer bias, interpretation of information on exposure or outcome for different patients). Besides, prospective studies are prone to bias from loss to follow-up or change in methods over time. In order to reduce selection bias, treating ophthalmologists were asked to sample consecutive patients, in a consecutive manner.

9.2 Setting

The study planned to involve 60 ophthalmology centers specialized for retina (retinologists) in France (clinics and hospitals, private and public).

Physician recruitment was made from a national database of relevant professionals from the OneKey file CEGEDIM. Participating physicians were doctors who agreed and returned a participation contract signed and valid. Age, sex, type of practice (private or public) and geographical location of the retinologist were collected in order to evaluate representativeness.

The participating centers had to include all patients who met eligibility criteria (i.e. patients with VA loss due to DME [in accordance with the local SmPC and HAS recommendation] and initiating treatment with IVT aflibercept) in a consecutive way until 400 patients were enrolled. The decision to prescribe the medication was separated from the decision to include the patient in the study

9.2.1 Withdrawal

In this observational study, withdrawal from the study was independent of the underlying therapy and did not affected the patient's medical care. Each patient could refuse to further participate or may withdraw from the study at any time and without giving a reason. After withdrawal of a patient from the study, no further data was collected for this patient. Data that has been collected so far were not

be used for any patient level analysis of study data. This includes safety data with the exception that data already captured in the company's safety database were kept. However, data which was relevant for primary outcomes could be displayed on an aggregated level to assess a potential bias. In case a patient wanted to withdraw the consent given earlier, s/he could inform his/her doctor and the site has to document the withdrawal in the Case Report Form. Patients were not be replaced after drop out. Using a patient identification list on site, each ophthalmologist has to provide an unique patient number to identify patients included consecutively in the study.

9.2.2 Replacement

Patients were not replaced after drop out. Handling of information that was retrieved after switch from aflibercept to other therapy were treated as for patients withdrawn.

9.2.3 Representativeness

The patients documented in this study were selected only based on eligibility according to inclusion and exclusion criteria as outlined in Section 9.2.2 and 9.2.3. No further selection criteria were applied. The study population is representative of the French DME patients followed in all types of ophthalmology centers (clinic, hospital, private or public) in real-life conditions.

9.2.4 Visits

The treating ophthalmologist or designated medical person (i.e. participating in this study) documented a baseline visit, initial visit, and follow-up visits for each patient in the eCRF. The study protocol did not define a schedule for the visits. Follow-up visits occurred during routine practice were scheduled at the discretion of the treating ophthalmologist.
All patient-based data required for the purposes of this study were collected, at least, at the initial visit, after each IVT injection during the first five months, at 6, 12 and 24 months after the first injection of IVT aflibercept.

Baseline / Initial visit

Once a patient was found eligible for inclusion according to inclusion and exclusion criteria, the investigator informed the patient about the study. This included discussing the consent form and asking the patient to read and - when agreeing to participate - sign the informed consent. This constituted the baseline visit. In addition, the initial visit was the first treatment day with IVT aflibercept administered at the clinic. If the first IVT aflibercept was done on the same day the informed consent form has been signed, the two visits were combined.

For all patients who do not participate to the study, a minimum of anonymisated information were collected in a non-inclusion register, reason of non-inclusion was documented if possible.

Data were returned to the sponsor by the investigator only after having received the patient's informed consent.

Follow-up visits

A follow-up visit was any contact of the treating ophthalmologist or medical staff with the patient regarding the Study eye only (not the fellow eye), regardless of whether or not an injection or any other treatment was given or the disease was only monitored related to DM/DR.

If a patient was seen by more than one ophthalmologist, the treating ophthalmologist or medical designee (i.e. participating in this study) had to collect all information.

Final Visit

The final visit was the last follow-up visit documented for the patient within the 24-month observation period. The observation period finished with the end of the safety follow-up (last IVT aflibercept + 30 days) or with the patient reaching the maximum observation period of 24 months whichever condition was fulfilled earlier. Switch of IVT aflibercept treatment to another type of treatment was a reason to end the observation period.. However, premature end of therapy did not automatically imply end of documentation: the patient had to be followed up until the end of the observation period or until no longer possible but at least 30 days after receiving the last therapy.

9.3 Subjects

The study population consists of patients with DME who have never been treated with aflibercept, and initiating treatment with IVT aflibercept per the ophthalmologist ‘s discretion. Patients with a diagnosis of DME were enrolled after the decision for treatment with IVT aflibercept was made by the investigator.

Two subgroups were considered for the study:

- Treatment naïve patient: Not previously treated with an anti-VEGF agent, macular laser photocoagulation or IVT steroid injection or steroid implant (steroids) in the study eye and initiating treatment with IVT aflibercept. A treatment naïve patient also shouldn’t have previously received any anti-VEGF agent or steroids injection or implant in the fellow eye.
- Previously treated patient: Already treated with any other treatment such as an anti-VEGF agent (other than IVT aflibercept), macular laser photocoagulation, IVT steroid injection or steroid implant in the study eye and initiating treatment with IVT aflibercept. Patients who have been previously treated with anti-VEGF agent, IVT steroid injection or steroid implant in the fellow eye are also considered as previously treated patients.

For patient initiating bilateral treatment with IVT aflibercept at the time of the inclusion in the study, eye with the worst visual acuity at baseline was considered as study eye.

9.3.1 Inclusion criteria

- Male or female aged 18 years or older
- Patient diagnosed with a visual impairment due to DME (as defined by HAS recommendation)
- Patients in whom a decision to treat with IVT aflibercept has been made independently of the patient enrollment in the study
- Patient diagnosed with type 1 or 2 diabetes mellitus
- Patient who has been given appropriate information about the study and who has given his/her written, informed consent

9.3.2 Exclusion criteria

- Patient with other retinal disease at the time of inclusion
- Patients currently being treated with IVT aflibercept. This study has only included patients new to IVT aflibercept.
- Systemic use of any anti / pro VEGF therapy

- Patient taking part in an interventional study

Inclusion and exclusion criteria follow the locally approved IVT aflibercept product information.

9.4 Variables

An overview of variables collected during the study is presented in Table 3 below. The treating ophthalmologist or medical staff documented the study-relevant data for each patient in the electronic case report form (CRF). The CRF is available upon request (see Table 23: List of stand-alone documents, Annex 1).

Table 3: Tabulated overview of variables collected during the study

Assessments	Baseline/initial visit Study eye and fellow eye	Follow-up visit(s) Study eye	Final visit Study eye
Visit date	X	X	X
Eligibility	X		
Patient information and consent	X		
Demography and clinical characteristics	X		
Medical & Medication History	X		
Co-morbidities	X		
Prior and concomitant medications	X	X	X
Visual Acuity (BCVA)	X	X	X
OCT anatomical measurements	X	X	X
FA anatomical measurements	X	X	X
Fundus photography anatomical measurements	X	X	X
Type of visit (monitoring, injection, combined) [a]		X	
Concomitant treatment for diabetes and adjunctive DME therapy	X	X	X
IVT aflibercept injection	X	X	X
IVT aflibercept retreatment criteria	X	X	X
Ocular and non-ocular Adverse Events	X	X	X [b]
Reasons for discontinuation of observation			X

[a] only for visits involving study eye
[b] patients could continue their treatment beyond the study period. Collection of AE had to continue up to 30 days after end of IVT aflibercept treatment or until 24 months whichever was earlier

9.4.1 Ophthalmological assessments

BCVA was recorded at the initial visit before the first injection of IVT aflibercept and at each follow-up visit, if available. The results of OCT (CRT and presence of fluid), FA and FP exams were recorded, if available, at the initial visit before the first injection of IVT aflibercept, at 12-month follow-up visit and at the final visit 24 months after the first injection of IVT aflibercept or at the date

the patient dropped out the study whichever applied first. All measures performed during the study were reported in the eCRF.

9.4.2 Demographics

For demographic/socio-demographic assessment, year of birth and gender were collected.

9.4.3 Disease history

Disease history describes any medical findings that were relevant to the underlying disease regarding the study eye (right, left, both) and were present before inclusion into the study. Findings and diagnosis meeting the criteria listed below were documented:

- Date of diagnosis
- Disease status at study start
- Involved eye
- Diabetes: type of diabetes, date of diagnosis, duration of diabetes, prior and current medication

As the DME is related to the diabetes pathology of patients, particular interest was taken for any diabetic medical history.

9.4.4 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that were present before start of therapy with IVT aflibercept, independent on whether or not they are still present. Amongst these co-morbidities, particular interest was given to:

- Hypertension
- Cardiovascular diseases
- Cerebrovascular diseases
- Hyperlipidemia
- Obesity

Co-morbidities were included in the Medical History / Concomitant Diseases section. The diagnosis, the start and the stop date were documented. Diseases or worsening of diseases occurring after the first injection with IVT aflibercept were documented as adverse events.

9.4.5 Prior, concomitant medications and adjunctive therapies

Any medication other than IVT aflibercept could be taken during the study at the decision of the investigator. However, any anti-VEGF medication in the study eye other than IVT aflibercept led to patient's withdrawal from the study.

All medications taken before study start (initiated and stopped before study start) were termed prior medication. All medications taken by the patients during the course of the study for any indication other than DME in addition to IVT aflibercept were termed concomitant medications. All concomitant medications taken during the study had to be documented. Other relevant concomitant therapies (including ophthalmological procedure) had to be documented, too. All DME treatments taken by the patient during the course of the study in addition to IVT aflibercept were termed adjunctive therapies.

Information collected for medication included trade name or INN, start date, Stop date/ongoing, dose, unit, frequency, administration route, indication, and if applicable, the eye(s) treated.

9.4.6 Exposure / treatment

In this observational study, the decision on the duration and dosage of treatment was solely at the discretion of the attending investigator. The medication was prescribed within the regular practice of the investigator. Commercially available product were used to treat the patients.

The treatment with IVT aflibercept had to comply with the recommendations written in the Product Monograph. The decision to assign a treatment to the patient was made before inclusion of the patient in the study.

Information to be documented on IVT aflibercept included:

- Date of injection
- Total injection volume administered [µL]
- Treatment/Study Eye

9.4.7 Laboratory data and vital signs

HbA1c values were collected at each visit if results were known by the ophthalmologist.

Blood pressure was collected at each visit if part of routine assessment by the ophthalmologist.

9.4.8 Adverse events

Ocular and non-ocular safety events were recorded.

An adverse event (AE) was any untoward medical occurrence in a patient administered a medicinal product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [7].

The term also covered laboratory findings or results of other diagnostic procedures that were considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

An AE could be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator product
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a product was implied by the use of the term “adverse event”.

An Adverse Reaction (AR) was defined as a response to a medicinal product which is noxious and unintended. An AR was any AE judged as having a reasonable suspected causal relationship to IVT aflibercept.

The assessment of the causal relationship between an AE and the administration of treatment was a clinical decision based on all available information at the time of the completion of the CRF. The assessment was based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answer was "yes" or "no".

An assessment of "no" included the existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site) and non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first product administration).

An assessment of "yes" indicated that there was a reasonable suspicion that the AE was associated with the use of the study treatment. Factors considered in assessing the relationship of the AE to study treatment included:

- The temporal sequence from product administration: the event occurred after the product was given. The length of time from product exposure to event was evaluated in the clinical context of the event.
- Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): subject's response after de-challenge or subjects response after re-challenge was considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: each event was evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: the other products the subject was taking or the treatment the subject received were examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment: the pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics were considered.

An AE was serious (SAE) if it met at least one of the following conditions:

- Resulted in death
- Was life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Resulted in persistent or significant disability or incapacity
- Was a congenital anomaly or birth defect
- Was medically important.

Death was usually the outcome of an underlying clinical event that causes it. Hence, it was the cause of death that was regarded as the SAE. The one exception to this rule is ‘sudden death’ where no cause was established. In this instance, ‘sudden death’ was regarded as the AE and ‘fatal’ as its reason for being ‘serious’.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization was considered as serious, unless the admission is planned before subject's inclusion in the study (i.e. elective or scheduled surgery) or ambulant (shorter than 12 hours) or part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease). However if an invasive treatment during any hospitalization fulfilled the criteria of 'medically important', it was reported as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically required a more stringent definition, the local regulation took precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, was regarded as a SAE when the mother was exposed to a medicinal product at any stage during conception or pregnancy or during delivery or the father was exposed to a medicinal product prior to conception.

Any adverse event was considered serious if it jeopardized the patient and required intervention to prevent another serious condition. Medically important events either referred to or were indicative of a serious disease state. Such reports warranted special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

9.5 Data sources and measurement

The treating ophthalmologist collected historic data (demographic and clinical characteristics) from medical records if available. Likewise, the treating ophthalmologist collected treatment related data during visits that take place in routine practice. Each patient was identified by a unique central patient identification code, which was only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel is able to identify the patient based on the patient identification code.

The data were entered by the treating ophthalmologist in the clinical database (eCRF). The treating ophthalmologists was trained to the eCRF during the Site Initiation Visit. The connection information to the secure eCRF website was sent by email by the data manager (login, password and the eCRF URL address). Data were stored on a server dedicated to the CRO in charge of data management.

BCVA was used to determine the visual acuity at each timepoint. If the ophthalmologist reported a BCVA value with another scale than the ETDRS, this information was converted into the right scale.

Several types of ophthalmological imaging system are used routinely in France as OCT, FA and FP. Exams were performed throughout the study according to routine clinical practice.

Starting with the first application of IVT aflibercept after enrollment into the study, all non-serious adverse events (AE) had to be documented on the AE Report Form or in the CRF / EDC system and forwarded to the MAH within 7 calendar days of awareness. All serious AEs (SAE) had to be documented and forwarded immediately (within 24 hours of awareness). For each AE, the investigator assessed and documented the seriousness, duration, relationship to product, action taken and outcome of the event.

If a pregnancy occurred during the study, although it is not a serious adverse event itself, it was documented and forwarded to the MAH within the same time limits as a serious adverse event. The result of a pregnancy was followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby was collected as adverse events.

The documentation of any AE / SAE ended with the completion of the observation period of the patient. However, any AE / SAE - regardless of the relationship and the seriousness - occurred up to 30 days after the last dose of IVT aflibercept within the study period was documented and forwarded to the MAH within the given timelines, even if this period goes beyond the end of observation. As long as the patient has not received any IVT aflibercept within the frame of the study AEs / SAEs were not documented as such in this observational study. However, they are part of the patient's medical history. For any serious product-related AE occurred after study end, the standard procedures that are in place for spontaneous reporting were followed.

For SAEs related to IVT aflibercept treatment, submission to the relevant authorities was done by the MAH.

9.6 Bias

The limitations in the analyses of data due to the observational nature of this study. Findings generated from this study are subject to biases, e.g. selection bias. Results for primary and secondary effectiveness variables have to be interpreted carefully because of the uncontrolled setting: Time periods between follow-up visits were much more variable than in controlled clinical studies in which a fixed visit schedule has to be maintained.

The aim of the study was to collect data on routine clinical practice. Comparison of the data and treatment patterns could only be performed with historical data from clinical or other observational studies, which was prone to bias and confounding. Potential sources and extent of bias are discussed in detail in this study report.

9.7 Study size

The Diabetic Retinopathy Clinical Research Network recently reported a comparison of IVT aflibercept, ranibizumab, and bevacizumab in patients with diabetic macular edema. In the IVT aflibercept group the mean visual acuity improved of 13+/-11 letters. A sample size of 385 produces a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 1,099 when the known standard deviation is 11,000.

Based on the DRCR net Protocol T study, in one year of treatment, it was planned to enroll 400 patients in total. Finally, 402 patients were enrolled over a period of 10 months.

9.8 Data transformation

Analysis sets and subgroups are presented in Section 9.9.2

9.8.1 Best corrected visual acuity

If the ophthalmologist reported a BCVA value with another scale than the ETDRS (letter count), this information was converted into the right scale according to the following formula:

$$ETDRS\ value\ \cong 85\ + 50\ \log_{10}(Decimal\ value)$$

The decimal values are equivalent to all Snellen results and to the Monoyer fractions. For the MAR and logMAR scales, we considered $logMAR = -\log_{10}(Decimal\,VA)$ or equivalently $Decimal\,VA = 10^{-logMAR}$. BCVA values were therefore converted according to the following formula:

$$ETDRS\ value \cong 85 + 50\ \log_{10}(Snellen\,VA)$$

$$ETDRS\ value \cong 85 + 50\ \log_{10}(Decimal\,VA)$$

$$ETDRS\ value \cong 85 + 50\ \log_{10}(Monoyer\,VA)$$

$$ETDRS\ value \cong 85 - 50\ logMAR$$

$$ETDRS\ value \cong 85 - 50\ \log_{10}(MAR)$$

Additional rules for low BCVA results were also considered for the scale conversion:

- If the result in the Snellen scale was 0 then the ETDRS score was 0. The same rules applied for the Decimal and Monoyer scales.
- If the converted results in the ETDRS scale was negative then the ETDRS score was 0 and if the converted results in the ETDRS scale was below five letters but still positive then the ETDRS score was 1.
- Finally, if the ophthalmologist recorded "Count fingers" or "Hand motion" or "Light perception" as a visual acuity result, the ETDRS score equivalent was 0.

9.8.2 IVT injections of aflibercept

The following data were calculated according to the formulas presented in the SAP

- Time between first and last injection (days)
- Mean number of injections received per patient
- Number of injections received per patient
- Patients who received exactly 3 injections within the first 3 months (Yes / No)
- Patient with at least one volume injected higher than 50 µL (Yes / No)
- Mean time between injections (days)
- Patients who received more than 8 injections within the first 12 months
- Total number of injections after 6, 12 and 24 months

9.8.3 Loading dose

A patient was considered as having received the loading dose if he/she received exactly 5 injections of IVT aflibercept in the study eye within the first 5 months, i.e. within 150 + 15 days from the first injection.

9.8.4 Prior and concomitant medications

Prior and concomitant medications were coded according to the WHO Drug Dictionary (WHO-DD) and were described according to the Anatomical Therapeutic Chemical (ATC) classification based on their therapeutic subgroup (ATC level 2) and chemical subgroup (ATC level 4).

All ophthalmological surgical procedures performed during the study are considered as concomitant.

9.9 Statistical methods

9.9.1 Main summary measures

9.9.1.1 General principles

All variables were analyzed descriptively with appropriate statistical methods.

Categorical variables were described by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum).

Continuous variables were described by absolute value and as change from initial visit per analysis time point, if applicable.

A two-sided 95% confidence interval was calculated when relevant.

9.9.1.2 Handling loss-to-follow-up premature discontinuation

Patients were not replaced after premature discontinuation. Handling of information that was retrieved after switch from IVT aflibercept to other therapy was treated as a patient withdrawn.

After withdrawal of a patient, no further data was collected for this patient. The previously collected data were retained unless patient requested to have their data deleted.

9.9.1.3 Data rules

Baseline values
Unless otherwise specified, the baseline values correspond to the data collected before the first injection of IVT aflibercept in the study eye for all patients.

However, a BCVA evaluation performed more than 3 months (=92 days) before the first EYLEA® injection was not considered as a baseline value. Moreover, an OCT, a FA or a FP evaluation performed more than 5 months (=152 days) before the first EYLEA® injection was not considered as a baseline value.

6-month values
For each efficacy endpoint evaluation (e.g. BCVA, CRT, etc.), 6-month values correspond to parameters assessed within the time frame of [4.5 months – 6.5 months[from the first IVT aflibercept injection in the study eye.

If two evaluations were performed within this time window, the evaluation closest to 6-month timepoint was taken into account.

9.9.2 Main statistical methods

The statistical evaluation was performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA) except when noticed otherwise. All computers programs were developed and validated according to ICTA PM Standard Operating Procedures (SOP).

Statistical analyses were explorative and descriptive nature. The study was not aimed to confirm or reject pre-defined hypotheses.

9.9.2.1 Assignment of analysis set

Full Analysis Set (FAS)

Patients included in the FAS are those who met eligibility criteria according to investigator, who received at least one injection of IVT aflibercept in the study eye and who had a BCVA evaluation at baseline for the study eye.

The study eye was defined as the eye for which IVT aflibercept was initiated at the initial visit. If both eyes were treated at that visit, only one eye defined by the physician according to the protocol was the study eye. Unless otherwise specified, analyses concern the study eye only.

Target FAS

Patients included in the target FAS are those included in the FAS and who have a BCVA evaluation at 12 months in the study.

Safety Set (SS)

Patients included in the SS are all patients having received at least one injection of IVT aflibercept whatever the injected eye.

9.9.2.2 Definition of subgroups

Two cohorts were considered for the analysis:

- Treatment naïve patients: patients not previously treated with an anti-VEGF agent, macular laser photocoagulation (laser) or intravitreal steroids injection or implant (steroids) in the study eye and initiating treatment with IVT aflibercept. A treatment naïve patient also shouldn't have previously received any anti-VEGF agent or steroids injection or implant in the other eye.
- Previously treated patients: patients already treated with any other treatment such as an anti-VEGF agent (other than IVT aflibercept), macular laser photocoagulation (laser), intravitreal steroids injection or implant (steroids) in the study eye and initiating treatment with IVT aflibercept.

For some criteria, additional classes were also defined:

- Loading dose: Received the loading dose / Did not receive the loading dose
- Received 3 injections exactly within the first 3 months / Did not receive exactly 3 injections within the first 3 months
- Over treated patients: Patients who received more than 8 injections within the first 12 months
- BCVA at inclusion: BCVA $\leq$ 24 letters / 24 letters < BCVA <70 letters / 70 letters $\leq$ BCVA
- BCVA at inclusion: BCVA $\leq$ 39 letters / 39 letters < BCVA < 60 letters / 60 letters $\leq$ BCVA
- BCVA at inclusion: BCVA $\leq$ 65 letters / BCVA > 65 letters

9.9.2.3 Demographics and other baseline characteristics

Demographics and other baseline characteristics are described as follows:

- Demographic data: age, gender,
- Physical and clinical examination: height, weight, body mass index, systolic and diastolic blood pressure, heart rate
- Smoking status
- Laboratory parameters: glycemia, HbA1c
- Medical history: hypertension, cardiovascular and cerebrovascular disease, diabetes and prior ophthalmological surgery
- DME history: DME diagnosis and previous DME treatments

- Ophthalmological assessment: BCVA, OCT results, FA results, FP results

9.9.2.4 Prior, concomitant medications and adjunctive therapies

Prior medications related to the study eye are presented in a frequency table according to ATC level 2 and 4.

Concomitant medications related to the study eye are presented in a frequency table overall and separately for ophthalmological and non-ophthalmological concomitant medications. An additional table presenting the frequency of indication for the concomitant medication is provided.

Concomitant ophthalmological surgical procedures were summarized as follows:

- No. and % of patients who experienced at least one concomitant ophthalmological surgery
- No. and % of patients who experienced at least one cataract surgery
- No. and % of patients who experienced at least one filtration surgery
- No. and % of patients who experienced at least one vitrectomy
- No. and % of patients who experienced at least one internal limiting membrane peeling
- No. and % of patients who experienced at least one other type of ophthalmological surgery

An additional table describes the frequency of each type of surgery and associated medical reason.

Type and frequency of adjunctive therapy used for DME was summarized. For each adjunctive therapy, all patients using this therapy after their inclusion in the study is described.

9.9.2.5 Primary outcome analysis

The primary endpoint was the mean change in BCVA between baseline and 12 months overall and according to treatment status (treatment naïve patients / previously treated patients) on the FAS and on the Target FAS.

Descriptive statistics of the mean change from baseline to 12 months, as well as the 95% confidence interval are presented. In addition, Student t-tests were provided to compare the mean BCVA at baseline and the mean BCVA at 12 months.

The BCVA change from baseline is also presented:

- according to the exact number of injection(s) received over the 12-month period (i.e. BCVA change for patients who received exactly one injection, for patients who received exactly 2 injections, etc.)
- after each injection (i.e. BCVA after the first injection, after the second injection, after the third injection etc.).

The analyses were repeated according to BCVA, CRT and HbA1c classes at inclusion.

For the BCVA missing values in the FAS, two different robustness analyses were performed (see section 9.9.3).

A graph corresponding to the evolution curve for the mean BCVA change throughout the study was issued separately for treatment naïve and previously treated patients. The evolution was assessed at each month for the first 6 months and afterwards at 12 and 24 months. Waterfall plots were produced for the mean change in BCVA at 12 months according to treatment status.

A frequency table was computed based on the qualitative variable defined with:

- BCVA loss higher than 15 letters
- BCVA loss between 10 and 14 letters

- BCVA loss between 5 and 9 letters
- BCVA loss between 1 and 4 letters
- BCVA improvement between 0 and 4 letters
- BCVA improvement between 5 and 9 letters
- BCVA improvement between 10 and 14 letters
- BCVA improvement higher than 15 letters.

9.9.2.6 Secondary outcome analysis

Change in BCVA

Analyses conducted for the primary endpoint (mean change in BCVA from baseline to 12 months) were repeated at 6 months and 24 months overall and according to treatment status on the FAS and on the Target FAS. The same two robustness analyses were conducted as for the primary outcome.

Change in CRT

The mean change in central retinal thickness (CRT) between baseline and 12 months is presented with the associated two sided 95% confidence interval overall and according to treatment status (treatment naive / previously treated) on the FAS. The CRT evolution throughout time is described using a graph.

Analyses were repeated for mean change from baseline to 6 months and 24 months.

The CRT missing values were imputed according to the same rules presented for the primary outcome.

Presence of fluid in OCT

Analyses were performed on the FAS overall and according to treatment status. The presence/absence of intra-retinal and sub-retinal fluid determined by optical coherence tomography (OCT) is described at baseline, 12 months and 24 months.

The analysis displays:

- No of patients who have intra-retinal fluid visible
- No of patients who have sub-retinal fluid visible
- No of patients with intra- and/or sub-retinal fluid visible
- No of patients with both intra-retinal and sub-retinal fluids visible

Change in FA/FP outcome

The fluorescein angiography (FA) and fundus photography (FP) outcomes between baseline and 24 months were presented on the FAS overall and according to treatment status (treatment naïve / previously treated) using shifts tables based on several criteria:

- The presence of any disease-related outcome
- The presence of micro-aneurysms and hemorrhages
- The presence of neovascularization of the disc
- The presence of new vessels elsewhere than the disc
- The presence of capillary leakage
- The presence of area of fluorescein leakage due to new vessels
- The presence of hard exudates
- The presence of soft exudates
- The presented of intra-retinal micro vascular abnormalities (IRMA)

The outcomes are presented separately for the FA and the FP.

DME monitoring

DME monitoring related to study eye during the course of the study was analyzed on the FAS overall and according to treatment status (treatment naïve / previously treated). Frequency tables are provided for the following parameters:

- No of patients with at least one visit 'injection only' at 6,12 and 24 months
- No of patients with at least one visit 'monitoring only' at 6,12 and 24 months
- No of patients with at least one combined visit at 6,12 and 24 months
- No of visits (Injection only / monitoring only / combined) over 6 months, over 12 months and over 24 months
- No of visits for diabetes (diabetologist)
- No of visits with OCT assessment after 6 months, after 12 months and after 24 months
- No of visits with FP after 6 months, after 12 months and after 24 months
- No of visits with FA after 6 months, after 12 months and after 24 months
- No of visits with VA assessment after 6 months, after 12 months and after 24 months

9.9.2.7 Safety analysis

Safety analysis (including AEs, vital signs and laboratory parameters) was performed on the SS.

Adverse events

AEs considered for this analysis are treatment-emergent adverse events (TEAE), i.e. AEs which occurred after the first injection of IVT aflibercept. For the ophthalmological AEs, the results concern both eyes without distinction.

Listings of all AE, all SAE, all treatment-related AE and all treatment-related SAE are provided. Additionally; a listing of all AE which are not TEAE recorded in the database is also presented.

An overview of ophthalmological AE and non-ophthalmological AE were provided separately. The number and percentage of patients with at least one AE and of the corresponding number of AEs is described including the following data:

- Any/All AE
- Any/All SAE
- Any/All AE related to EYLEA®
- Any/All AE related to procedure
- Any/All AE leading to treatment withdrawal
- Any/All SAE related to EYLEA®
- Any/All SAE leading to treatment withdrawal
- Any/All SAE leading to death

AEs and SAEs were also summarized in frequency tables according to System organ class (SOC) and Preferred terms (PT).

Vital signs

Blood pressure (systolic and diastolic) and heart rate were summarized at baseline, 12 months and 24 months. Change at 12 months and 24 months from baseline were analyzed.

Laboratory parameters

Glycemia and HbA1c level were summarized at baseline, 12 months and 24 months. Change at 12 months and 24 months from baseline were analyzed.

9.9.3 Missing values

Missing data for BCVA were replaced according to 2 different imputation methods.

- Median imputation: in each subgroup (Treatment naive patients / Previously treated patients), the median for the 6-month BCVA were computed and the 6-month BCVA missing values were replaced by the subgroup median depending on the patient subgroup.
- Markov Chain Monte Carlo (MCMC) imputation: in case of missing BCVA at 6 months, the missing values were replaced according to the patient's previous BCVA results based on a MCMC algorithm with 10000 iterations.

In case of incomplete date for the DME diagnosis, the missing information were handled as follows:

- If both days and months were missing, the date was imputed with the 1st July unless the year was the same as the inclusion's year. In this case, the missing information was replaced by the 1st January.
- If only the day is missing, it was replaced by 15 unless the month and year corresponded to the inclusion ones. In this case, the day was replaced by the 1st of the month.

Regarding the starting date of an adverse event (AE), if the date was missing, AE was considered by default as Treatment Emergent (TEAE), except in particular situations where the available information was sufficient to ensure that the AE was not emergent.

For the date of diabetes diagnosis; if only the year was recorded then the time since the diagnosis was computed using the year of diagnosis minus the year of first IVT aflibercept injection in the study eye.

For all the other variables no missing data imputation was performed.

Of note, all modalities "Unknown' were considered as missing values for the percentage computations.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

9.10.1 Data quality

Before study start at the sites, all investigators were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. During site initiation, investigators had the opportunity to discuss and develop a common understanding of the study protocol and the CRF. Once trained, investigators were to ensure the quality of the data reported in the CRFs.

EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer was performed by ICTA PM.

All outcome variables and covariates were recorded in a standardized CRF. After data entry, missing or implausible data were queried and the data were validated. A check for multiple documented patients was done. Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The DMP is available upon request (see Table 23: List of stand-alone documents, Annex 1).

Medical Review of the data was performed according to the Medical Review Plan (MRP). The purpose of the Medical Review was to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review are described in the MRP, which is available upon request (see Table 23: List of stand-alone documents, Annex 1).

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for capturing patient documentation (eCRF) were validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [8]. The documentation is available upon request (see Table 23: List of stand-alone documents, Annex 1).

9.10.2 Quality review

In a subset of patients (at least 20% of all patients) source data verification was conducted. The purpose was to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors had access medical records on site for data verification. Detailed measures for quality reviews have been described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 23: List of stand-alone documents, Annex 1).

9.10.3 Storage of records and archiving

The treating ophthalmologists participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and / or local authorities. It was recommended to also store documents for a retention period of at least 10 years.

ICTA will send to Bayer, the database and statistical programming performed to generate results; they will be stored on Bayer environment.

9.10.4 Certification/qualification of external parties

Not applicable

10. Results

This section presents the results from the first interim analysis.

10.1 Participants

From 15 SEP 2016 to 05 JUL 2017, 61 ophthalmologists participated in the study and contributed 402 patients, 364 (90.5%) of whom are included in the FAS.

Disposition of patients and main reason for premature discontinuation are summarized in Table 4 and Table 5.

Thirty-two (8.8%) patients from the FAS terminated the study prematurely, mainly to switch to another treatment (N=16; 6.6%). Among the 16 patients who prematurely terminated the study for another reason than switching to another treatment, 5 patients were lost to follow-up, 4 patients changed of treating ophthalmologist, 3 patients died, 2 patients withdrew their consent and 2 patients stopped the study according to treating ophthalmologist decision. None of the deaths were related to EYLEA® treatment (see Section 10.6 Adverse events/adverse reactions). Among the patients who switched to another treatment, only one patient switched because of an adverse event; the 15 remaining switched because of a lack of efficacy or consecutively to treating ophthalmologist decision. A large majority (15 patients; 93.8%) switched to Ozurdex.

At the time of the data cut-off of the interim analysis (19 FEB 2018), 283 patients (146 treatment naïve patients and 137 previously treated patients) met criteria to be included in the FAS and had been followed at least 6 months within the study. Results presented in this interim OS report refer to these 283 patients.

Table 4: Patient disposition

	Enrolled N = 402
Patients enrolled in the study	402
Patients included in the Safety Set (SS)	386 (96.0%)
Reason for exclusion from the SS	16
No treatment injection in any of the eye	16 (100.0%)
Patients included in the Full Analysis Set (FAS)	364 (90.5%)
Reason for exclusions from the FAS [a]	38
Screening failure	18 (47.4%)
No BCVA evaluation at baseline	26 (68.4%)
No treatment injection in the study eye	17 (44.7%)
Patients excluded from the SS	16 (42.1%)
Patient included in the FAS and followed for at least 6 months [b]	283 (70.4%)
Patient included in the FAS and with a BCVA available at 6 months [c]	217 (54.0%)

[a] a patient can have several reasons for exclusion of the analysis set
[b] patients with a BCVA evaluation or a CRT evaluation or an injection or a visit in the 4.5 months - 6.5 months time windows after the first EYLEA® injection
[c] patients with a BCVA evaluation in the 4.5 months - 6.5 months time windows after the first EYLEA® injection
Reference: Table 1.1 in Annex 2: Tables, Figures and Listings

Table 5: Early discontinuation

		FAS N = 364
Patients who terminated the study prematurely	N (%)	32 (8.8%)
Early termination primary reason	N	32
Change of treating ophthalmologist	N (%)	4 (12.5%)
Death	N (%)	3 (9.4%)
Withdrawal of consent/Patient decision	N (%)	2 (6.3%)
Lost to follow-up	N (%)	5 (15.6%)
Treating ophthalmologist decision	N (%)	2 (6.3%)
Switch to another treatment	N (%)	16 (50.0%)
Switch to Ozurdex	N (%)	15 (4.1%)
Switch to Lucentis	N (%)	1 (0.3%)
Main reason for switching to another treatment	N	16
Lack of efficacy / no responder	N (%)	10 (62.5%)
Treating ophthalmologist decision	N (%)	5 (31.3%)
Adverse even	N (%)	1 (6.3%)

Reference: Table 1.3 in Annex 2: Tables, Figures and Listings

10.2 Descriptive data

10.2.1 Demographic and other baseline characteristics

10.2.1.1 General baseline characteristics and medical history

Tables displaying demographic and other baseline characteristics are presented in Annex 2: Tables, Figures and Listings, Tables 2.2.2.1 to 2.2.2.5 (demographics, physical and clinical examination), Tables 2.2.3.1.1, 2.2.3.2.1, 2.2.3.3.1, 2.2.3.3.2 and 2.2.5.1 (medical and surgical history).

General baseline characteristics are summarized in Table 6.

Patients had mean (±SD) age of 65.6 ± 11.3 years (range, 19-90 years) and were slightly more male (54.8%). Less than 10% of patients were current smokers and 30.8% were former smokers.

Mean (±SD) body mass index was 29.6 ± 6.1 kg/m² and mean (±SD) blood pressure was 141 ± 19 / 77 ± 11 mmHg. These values are slightly over the normal values but are consistent with epidemiological data related to DME patients. Moreover, these parameters did not significantly differ between treatment naïve and previously treated patients.

Medical history related to hypertension, cardiovascular and cerebrovascular disease is detailed in Table 2.2.3.1.1 in Annex 2: Tables, Figures and Listings.

Table 6: General baseline characteristics

		Treatment Naïve N = 146	Previously treated N = 137	Total N = 283
Age (years)	N	146	137	283
	Mean ± SD	64.2 ± 12.0	67.2 ± 10.3	65.6 ± 11.3
	Median	65.0	67.0	66.0
	Q1 ; Q3	57.0 ; 73.0	61.0 ; 74.0	59.0 ; 74.0
	Min ; Max	19 ; 90	31 ; 91	19 ; 91
Gender (male)	N (%)	82 (56.2%)	73 (53.3%)	155 (54.8%)
Smoking status	N	125	115	240
	Missing values	21	22	43
Never	N (%)	74 (59.2%)	70 (60.9%)	144 (60.0%)
Former	N (%)	36 (28.8%)	38 (33.0%)	74 (30.8%)
Current	N (%)	15 (12.0%)	7 (6.1%)	22 (9.2%)
BMI (kg/m²)	N	93	90	183
	Missing values	53	47	100
	Mean ± SD	29.4 ± 6.7	29.8 ± 5.5	29.6 ± 6.1
	Median	27.7	29.1	28.7
	Q1 ; Q3	24.9 ; 32.7	26.4 ; 33.3	25.5 ; 32.9
	Min ; Max	17 ; 50	18 ; 46	17 ; 50
SBP (mmHg)	N	54	62	116
	Missing values	92	75	167
	Mean ± SD	141.2 ± 19.0	141.7 ± 19.1	141.5 ± 19.0
	Median	141.0	140.0	140.0
	Q1 ; Q3	122.0 ; 160.0	130.0 ; 151.0	130.0 ; 154.5
	Min ; Max	109 ; 179	100 ; 200	100 ; 200
DBP (mmHg)	N	54	61	115
	Missing values	92	76	168
	Mean ± SD	77.4 ± 12.2	77.4 ± 10.6	77.4 ± 11.3
	Median	80.0	80.0	80.0
	Q1 ; Q3	70.0 ; 90.0	70.0 ; 80.0	70.0 ; 84.0
	Min ; Max	44 ; 100	50 ; 100	44 ; 100

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure
Reference: Tables 2.2.2.1 to 2.2.2.4 in Annex 2: Tables, Figures and Listings

Diabetes baseline characteristics are summarized in Table 7.

Mean (±SD) time since diabetes diagnosis was 18.0 ± 12.6 years for treatment naïve patients and 19.2 ± 10.8 years for previously treated patients.

Mean (±SD) glycemia was 14.2 ± 17.4 mmol/L in treatment naïve patients compared to 8.8 ± 8.9 mmol/L in previously treated patients. In both subgroups, mean and median glycemia were over the normal values and show that more than 1 in 2 subjects did not have their sugar blood under control at the time of their last glycemia test according to the definition of diabetes as established by the WHO (i.e. glycemia higher than 6.3 mmol/L).Mean (±SD) HbA1c level was 7.7 ± 1.3% which reflect the underlying condition of the patients suffering from diabetes (>6%). However, mean HbA1c did not significantly differ in treatment naïve and previously treated patients.

Table 7: Diabetes baseline characteristics

		Treatment Naïve N = 146	**Previously treated N = 137**	**Total N = 283**
Time since diabetes diagnosis (years)	N	139	124	263
	Missing values	7	13	20
	Mean ± SD	18.0 ± 12.6	19.2 ± 10.8	18.6 ± 11.8
	Median	16.0	18.5	17.0
	Q1 ; Q3	9.0 ; 25.0	11.0 ; 25.5	10.0 ; 25.0
	Min ; Max	0 ; 50	2 ; 63	0 ; 63
Glycemia (mmol/L)	N	31	29	60
	Missing values	115	108	223
	Mean ± SD	14.2 ± 17.4	8.8 ± 8.9	11.6 ± 14.1
	Median	8.6	7.1	7.6
	Q1 ; Q3	6.0 ; 11.1	5.4 ; 8.9	5.7 ; 9.7
	Min ; Max	4 ; 83	1 ; 52	1 ; 83
HbA1c (%)	N	93	82	175
	Missing values	53	55	108
	Mean ± SD	7.8 ± 1.4	7.6 ± 1.2	7.7 ± 1.3
	Median	7.5	7.5	7.5
	Q1 ; Q3	6.9 ; 8.4	6.6 ; 8.4	6.7 ; 8.4
	Min ; Max	6 ; 13	5 ; 11	5 ; 13

Reference: Tables 2.2.2.5 and 2.2.3.1.1 in Annex 2: Tables, Figures and Listings

History of ophthalmological surgery is summarize in Table 8.

Overall 106 (39.6%) patients had experienced at least one previous ophthalmological surgery, mainly cataract surgery (95 patients; 35.4%). Prior cataract surgery was more frequent in patients previously treated for DME (45.1% vs. 25.9% in treatment naïve patients).

Table 8: Prior ophthalmological surgery

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
Prior ophthalmological surgery [a]	N	135	133	268
	Missing values	11	4	15
	N (%)	42 (31.1%)	64 (48.1%)	106 (39.6%)
At least one prior cataract surgery	N (%)	35 (25.9%)	60 (45.1%)	95 (35.4%)
At least one prior filtration surgery	N (%)	1 (0,7%)	0 (0.0%)	1 (0.4%)
At least one prior vitrectomy	N (%)	4 (3.0%)	5 (3.8%)	9 (3.4%)
At least one prior ILM peeling	N (%)	2 (1.5%)	3 (2.3%)	5 (1.9%)
At least one other prior ophthalmological surgery	N (%)	9 (6.7%)	1 (0.8%)	10 (3.7%)

[a] prior ophthalmological surgery related to study eye only
ILM: internal limiting membrane
Reference: Tables 2.2.3.2.1 in Annex 2: Tables, Figures and Listings

DME history (including prior DME treatments received in the study eye) is summarized in Table 9.

Mean (±SD) time since DME diagnosis for study eye was 7.6 ± 19.5 months in treatment naïve patients and 37.6 ± 36.6 in previously treated patients. Median time were 1.0 month and 24.9 months, respectively.

Among previously treated patients (N=137), 88 (67.2%) patients had been previously treated with IVT anti-VEGF in the study eye (mainly with Lucentis [84 patients], 84 (64.1%) patients had been previously treated with laser (mainly pan-photocoagulation laser [58 patients]) for the study eye and 32 (24.6%) patients had been previously injected with intraocular steroids in the study eye.

Table 9: DME history related to the study eye

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
Time since DME diagnosis (months) [a]	N	144	137	281
	Missing values	2	0	2
	Mean ± SD	7.6 ± 19.5	37.6 ± 36.6	22.2 ± 32.7
	Median	1.0	24.9	8.4
	Q1 ; Q3	0.3 ; 4.0	11.3 ; 50.9	0.9 ; 29.8
	Min ; Max	0 ; 120	0 ; 222	0 ; 222
Time since last DME treatment (months) [a]	N	N/A	125	N/A
	Missing values		12	
	Mean ± SD		8.9 ± 13.4	
	Median		4.1	
	Q1 ; Q3		1.6 ; 8.5	
	Min ; Max		0 ; 72	

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
Photocoagulation laser [a]	N	N/A	131	277
	Missing values		6	6
Prior Laser (all type)	N (%)		84 (64.1%)	84 (30.3%)
Macular	N (%)		23 (17.6%)	23 (8.3%)
Pan-photocoagulation	N (%)		58 (44.3%)	58 (20.9%)
Macular grid	N (%)		3 (2.3%)	3 (1.1%)
Intraocular steroids [a]	N	N/A	130	276
	Missing values		7	7
Prior IVT steroid	N (%)		32 (24.6%)	32 (11.6%)
Anti-VEGF treatment [a]	N	N/A	131	277
	Missing values		6	6
Prior IVT anti-VEGF	N (%)		88 (67.2%)	88 (31.8%)
Lucentis only	N (%)		77 (58.8%)	77 (27.8%)
Lucentis and Avastin	N (%)		7 (5.3%)	7 (2.5%)
Avastin only	N (%)		3 (2.3%)	3 (1.1%)
Avastin and Macugen	N (%)		1 (0.8%)	1 (0.4%)

IVT: intra-vitreal; VEGF: vascular endothelial growth factor; [a] related to study eye
Reference: Tables 2.2.3.3.2 in Annex 2: Tables, Figures and Listings

10.2.1.2 Baseline ophthalmological conditions

Tables displaying baseline ophthalmological conditions are presented in Annex 2: Tables, Figures and Listings, Tables 2.2.3.4.1 to 2.2.3.4.4.

Visual and anatomic baseline characteristics are summarized in Table 10.

Baseline BCVA and OCT assessments (CRT and presence of retinal fluid) were similar in treatment naïve patients and previously treated patients. Mean (±SD) baseline BCVA was 60.7 ± 15.5 letters with 59.0% of patients presenting with a BCVA ≤65 letters, and mean CRT was 449.4 ± 129.9 µm with 77.4% of patients presenting with a CRT ≥ 350 µm. Almost all patients (95.8%) had intra-retinal fluid visible on OCT and 28.6% had sub-retinal fluid visible. The only significant difference between the 2 cohorts concerns history of cataract surgery that was more frequent in previously treated patients (45.1% vs. 25.9% in treatment naïve patients).

Table 10: Visual and anatomic baseline characteristics

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
BCVA (letter count)	N	146	137	283
	Mean ± SD	62.6 ± 14.1	58.8 ± 16.7	60.7 ± 15.5
	CI (95%)	[60.3 ; 64.9]	[56.0 ; 61.6]	[58.9 ; 62.5]
	Median	65.0	64.0	65.0
	Q1 ; Q3	54.0 ; 73.0	50.0 ; 69.0	53.0 ; 72.0
	Min ; Max	9 ; 85	0 ; 83	0 ; 85
≤ 24 letters	N (%)	3 (2.1%)	6 (4.4%)	9 (3.2%)
]24 - 73[letters	N (%)	101 (69.2%)	104 (75.9%)	205 (72.4%)
≥ 73 letters	N (%)	42 (28.8%)	27 (19.7%)	69 (24.4%)
≤ 39 letters	N (%)	13 (8.9%)	19 (13.9%)	32 (11.3%)
]39 - 60[letters	N (%)	35 (24.0%)	37 (27.0%)	72 (25.4%)
≥ 60 letters	N (%)	98 (67.1%)	81 (59.1%)	179 (63.3%)
≤ 65 letters	N (%)	82 (56.2%)	85 (62.0%)	167 (59.0%)
> 65 letters	N (%)	64 (43.8%)	52 (38.0%)	116 (41.0%)
CRT (µm)	N	138	128	266
	Missing values	5	8	13
	Mean ± SD	444.1 ± 121.1	455.1 ± 139.0	449.4 ± 129.9
	Median	425.5	424.5	425.5
	Q1 ; Q3	355.0 ; 517.0	352.0 ; 522.5	352.0 ; 519.0
	Min ; Max	229 ; 820	212 ; 980	212 ; 980
≤ 250 µm	N (%)	1 (0.7%)	2 (1.6%)	3 (1.1%)
] 250 - 350 [µm	N (%)	30 (21.7%)	27 (21.1%)	57 (21.4%)
[350 - 400] µm	N (%)	29 (21.0%)	28 (21.9%)	57 (21.4%)
> 400 µm	N (%)	78 (56.5%)	71 (55.5%)	149 (56.0%)
Sub-retinal fluid visible on OCT	N	132	123	255
	Missing values	11	13	24
	N (%)	41 (31.1%)	32 (26.0%)	73 (28.6%)
Intra-retinal fluid visible on OCT	N	134	125	259
	Missing values	9	11	20
	N (%)	128 (95.5%)	120 (96.0%)	248 (95.8%)
Both fluids visible on OCT	N	132	123	255
	Missing values	11	13	24
	N (%)	36 (27.3%)	28 (22.8%)	64 (25.1%)
Lens status	N	135	133	268
	Missing values	11	4	15
Prior cataract surgery	N (%)	35 (25.9%)	60 (45.1%)	95 (35.4%)

Reference: Tables 2.2.4.1, 2.2.4.2, 2.2.3.2.1 and 3.2.1 in Annex 2: Tables, Figures and Listings

10.2.2 Concomitant and adjunctive therapies

Tables displaying concomitant and adjunctive therapies are presented in Annex 2: Tables, Figures and Listings, Tables 2.2.5.2 to 2.2.5.7.

An overview of concomitant medications (i.e. any medication taken in addition to the product for any indication other than DME, either initiated before study start or during the study) is presented in Table 11. Within this interim analysis, only treatment coded through the coding process are considered.

A large majority of patients (86.2%) received at least one concomitant medication during the 6 months follow-up, mainly non ophthalmological medications (82.0%). Less than one quarter of patients (20.9%) received a concomitant ophthalmological medication, mainly sympathomimetics in glaucoma therapy (5.0%), antiinfectives (4.2%) and beta blocking agents (3.9%). All ophthalmological concomitant treatment are detailed according to their ATC level 2 and 4 in Annex 2: Tables, Figures and Listings, Tables 2.2.5.3.

Table 11: Overview of concomitant medication

		Treatment naïve N = 146	**Previously treated N = 137**	**Total N = 283**
At least one concomitant medication [a]	N (%)	127 (87.0%)	117 (85.4%)	244 (86.2%)
At least one ophthalmological concomitant medication [a]	N (%)	27 (18.5%)	32 (23.4%)	59 (20.9%)
At least one non ophthalmological concomitant medication	N (%)	121 (82.9%)	111 (81.0%)	232 (82.0%)

[a] ophthalmological concomitant medications only concern the study eye
Reference: Tables 2.2.5.2 in Annex 2: Tables, Figures and Listings

Concomitant ophthalmological surgical procedures (i.e. experienced during the 6-month follow-up period) are summarized in Table 12.

Overall 20 (7.1%) patients experienced at least one concomitant ophthalmological surgery within the first 6 months of follow-up, mainly cataract surgery (12 patients).

Table 12: Concomitant ophthalmological surgery

		Treatment naïve N = 146	**Previously treated N = 137**	**Total N = 283**
Concomitant ophthalmological surgery [a]	N (%)	12 (8.2%)	8 (5.8%)	20 (7.1%)
At least one cataract surgery	N (%)	7 (4.8%)	5 (3.6%)	12 (4.2%)
At least one filtration surgery	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
At least one vitrectomy	N (%)	0 (0.0%)	1 (0.7%)	1 (0.4%)
At least one ILM peeling	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
At least one other ophthalmological surgery	N (%)	5 (3.4%)	2 (1.5%)	7 (2.5%)

ILM: internal limiting membrane; [a] ophthalmological concomitant surgery only concern the study eye
Reference: Table 2.2.5.5 in Annex 2: Tables, Figures and Listings

Adjunctive therapies (i.e. DME treatment, other than IVT aflibercept, received by the patient during the course of the study) are summarized in Table 13.

Overall 46 (16.3%) patients have received at least one adjunctive therapy during the first 6 months follow-up, mainly laser therapy (37 patients). Ten patients (3.5%) received at least one adjunctive medication, and although corticosteroids are not part of the standard of care for DME anymore, corticosteroids were the most frequent adjunctive medication administered (7 patients). However, considering this interim analysis (i.e. ongoing data collection), the frequency of adjunctive medication may have been overestimated as an adjunctive treatment may have been started without certainty about continuing EYLEA® treatment.

Table 13: Adjunctive therapies

		Treatment naïve N = 146	**Previously treated N = 137**	**Total N = 283**
At least one adjunctive therapy [a]	N (%)	20 (13.7%)	26 (19.0%)	46 (16.3%)
At least one adjunctive laser therapy [b]	N (%)	17 (11.6%)	20 (14.6%)	37 (13.1%)
Macular	N (%)	4 (2.7%)	2 (1.5%)	6 (2.1%)
Pan-photocoagulation	N (%)	14 (9.6%)	18 (13.1%)	32 (11.3%)
Macular grid	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
At least one adjunctive medication [b]	N (%)	3 (2.1%)	7 (5.1%)	10 (3.5%)
Anti-inflammatory agents, corticosteroids	N (%)	2 (1.4%)	5 (3.6%)	7 (2.5%)
Antineovascularisation Agents	N (%)	0 (0.0%)	2 (1.5%)	2 (0.7%)
Carbonic Anhydrase Inhibitors	N (%)	1 (0.7%)	0 (0.0%)	1 (0.4%)

[a] adjunctive therapies only concern the study eye
[b] a patient may have received several adjunctive treatments
Reference: Tables 2.2.5.6 and 2.2.5.7 and Listing 2.2.5.1 in Annex 2: Tables, Figures and Listings

10.2.3 Treatment exposure

Tables displaying condition of use of EYLEA® treatment are presented in Annex 2: Tables, Figures and Listings, Tables 3.1.1, 3.1.2, 3.2.1 and 3.2.2.

Data related to the number of injections received per patient in the study eye during the first 6-month follow-up period are summarized in Table 14 and Figure 1.

Mean (±SD) number of injections received per patient during the first 6-month follow-up period was 5.3 ± 1.2 injections in treatment naïve patients and 4.8 ± 1.3 injections in previously treated patients. Median number of injections was 5 in both cohorts. Overall, 41.7% of patients received the loading dose (i.e. 5 consecutive monthly injections, according to the SmPC) but 72.8% received at least 5 injections during the first 6-month follow-up period. It has to be noted that only 4 (1.4%) patients received more than 7 injections over the 6-month period.

Table 14: Number of injections of IVT aflibercept

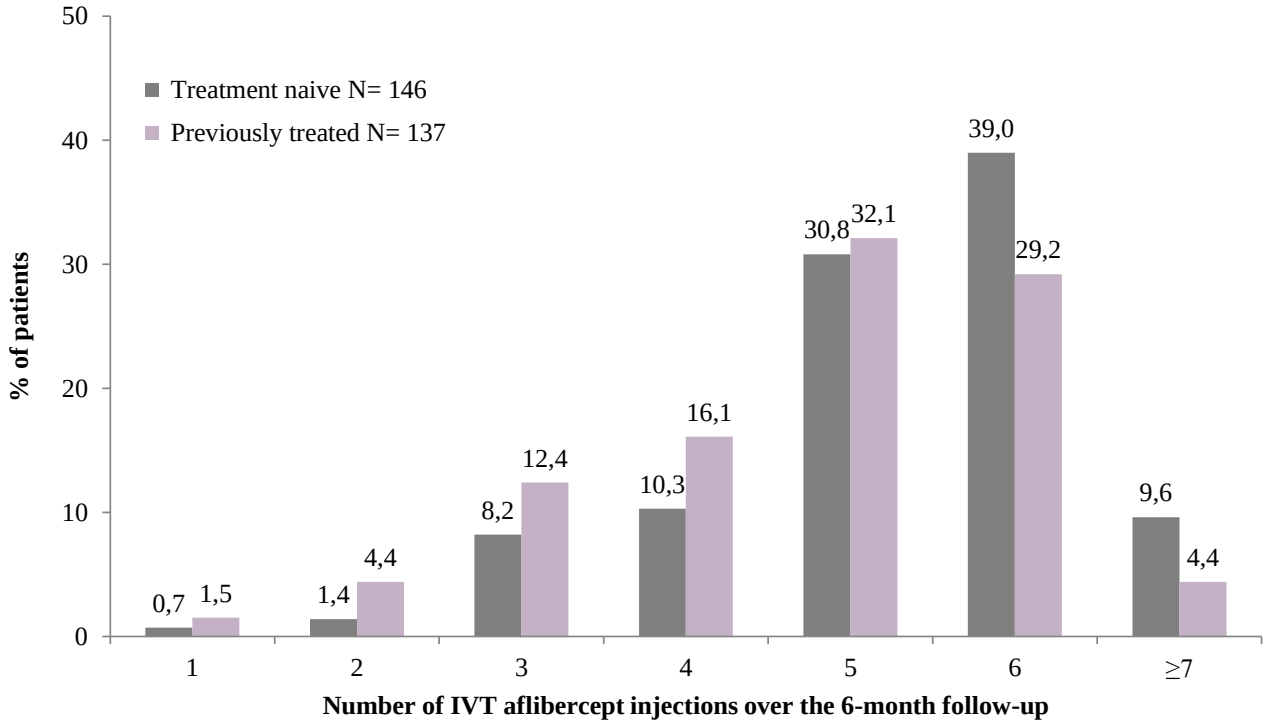
		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
Number of injections received per patient [a]	N	146	137	283
	Mean ± SD	5.3 ± 1.2	4.8 ± 1.3	5.0 ± 1.3
	Median	5.0	5.0	5.0
	Q1 ; Q3	5.0 ; 6.0	4.0 ; 6.0	4.0 ; 6.0
	Min ; Max	1 ; 8	1 ; 8	1 ; 8
Number of injections exactly received per patient	N	146	137	283
	Exactly 1	1 (0.7%)	2 (1.5%)	3 (1.1%)
	Exactly 2	2 (1.4%)	6 (4.4%)	8 (2.8%)
	Exactly 3	12 (8.2%)	17 (12.4%)	29 (10.2%)
	Exactly 4	15 (10.3%)	22 (16.1%)	37 (13.1%)
	Exactly 5	45 (30.8%)	44 (32.1%)	89 (31.4%)
	Exactly 6	57 (39.0%)	40 (29.2%)	97 (34.3%)
	Exactly 7	12 (8.2%)	4 (2.9%)	16 (5.7%)
	Exactly 8	2 (1.4%)	2 (1.5%)	4 (1.4%)
Loading dose received [b]	N	146	137	283
	N (%)	69 (47.3%)	49 (35.8%)	118 (41.7%)
Patient who received exactly 3 injections within the first 3 months [c]	N	146	137	283
	N (%)	81 (55.5%)	68 (49.6%)	149 (52.7%)

[a] only injections performed within the time frame [4.5 – 6.5[months were considered

[b] a patient was considered as having received the loading dose if he/she received exactly 5 injections of IVT aflibercept in the study eye within the first 5 months, i.e. within 150 + 15 days from the first injection. Patients who were followed less than 165 days were considered as having not received the loading dose[c] patients who received exactly 3 injections within the timeframe [0 – 30.4375*3] days from the first injection

Reference: Table 3.2.1 in Annex 2: Tables, Figures and Listings

Figure 1: Treatment frequency



Reference: Table 3.2.1 in Annex 2: Tables, Figures and Listings

Main reason for permanent discontinuation of EYLEA® is summarized in Table 15.

During the first 6-month follow-up period, 15 (5.3%) patients discontinued EYLEA® permanently, mainly to switch to another treatment (9 patients). Ozurdex was the treatment mainly prescribed (4 patients). Two patients permanently stopped EYLEA® consecutively to an adverse event: skin reaction possibly related to EYLEA® injection for one patient and myocardial infarction leading to death but not related to EYLEA® for the other patient (see Listing 3.2.1 in Annex 2: Tables, Figures and Listings).

Table 15: Permanent discontinuation of EYLEA®

		Treatment naïve N = 146	**Previously treated N = 137**	**Total N = 283**
Main reason for EYLEA® permanent discontinuation	N	9	6	15
Adverse event	N (%)	1 (11.1%)	1 (16.7%)	2 (13.3%)
Withdrawal of consent/Patient decision	N (%)	1 (11.1%)	0 (0.0%)	1 (6.7%)
Treating ophthalmologist decision	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Switch to another treatment	N (%)	5 (55.6%)	4 (66.7%)	9 (60.0%)
Missing data	*N*	*4*	*0*	*4*
Ozurdex	*N (%)*	*1 (100.0%)*	*3 (75.0%)*	*4 (80%)*
Lucentis	*N (%)*	*0 (0.0%)*	*1 (25.0%)*	*1 (20%)*
Other reason	N (%)	2 (22.2%)	1 (16.7%)	3 (20.0%)

Reference: Table 3.2.1 and Listing 3.2.2 in Annex 2: Tables, Figures and Listings

10.3 Outcome data

At the time of the interim analysis, 283 patients have achieved 6 months follow-up, i.e. patients with a BCVA evaluation or a CRT evaluation or an injection or a follow-up visit within the time window [4.5 months - 6.5 months] after the first EYLEA® injection (see section 10.1, Table 4).

Table 16 presents the number of patients with BCVA and CRT recorded at 6 months.

Table 16: Outcome data

		Treatment naïve N = 146	**Previously treated N = 137**	**Total N = 283**
Baseline BCVA available	N (%)	146 (100%)	137 (100%)	283 (100%)
6-month BCVA available	N (%)	113 (77.4%)	104 (75.9%)	217 (76.7%)
Baseline CRT available	N (%)	138 (94.5%)	128 (93.4%)	266 (94.0%)
6-month CRT available	N (%)	51 (34.9%)	63 (46.0%)	114 (40.3%)

Reference: Tables 4.1.1 and 5.2.1 in Annex 2: Tables, Figures and Listings

10.4 Main results

10.4.1.1 Change in the BCVA at 6 months

BCVA (in EDTRS letters) at baseline and at 6 months are presented in Annex 2: Tables, Figures and Listings, Tables 4.1.1, 4.2.1 and 4.3.1.

Out of the 283 patients followed 6 months from the first IVT aflibercept injection, 217 patients had BCVA available at 6 months (i.e, 66 patients had no BCVA available at 6 months).

Table 17, Figure 2, More than half of patients (54.8%) achieved an improvement in BCVA of at least 1 line (5 letters) 6 months after the first injection of IVT aflibercept, with 35.0% achieving a gain of at least 2 lines, and 22.3% achieving a gain of at least 3 lines. Results are quite similar in both subgroups (treatment naïve and previously treated patients) (see Figure 3).

Figure 3 and Figure 4 present change in BCVA at 6 months using median imputation for missing BCVA at 6 months.

Mean (±SD) change in BCVA at 6 months was 8.5 ± 11.9 letters in treatment naïve patients vs. 6.4 ± 13.4 letters in previously treated patients. Median change were respectively +8.0 and +4.0 letters. More than half of patients (54.8%) achieved an improvement in BCVA of at least 5 letters (1 line) 6 months after the first injection of IVT aflibercept, with 35.0% achieving a gain of at least 2 lines, and 22.3% achieving a gain of at least 3 lines. Very few patients (3.9%; 11 patients) lost more than 2 lines and most of them (8 patients) were previously treated patients.

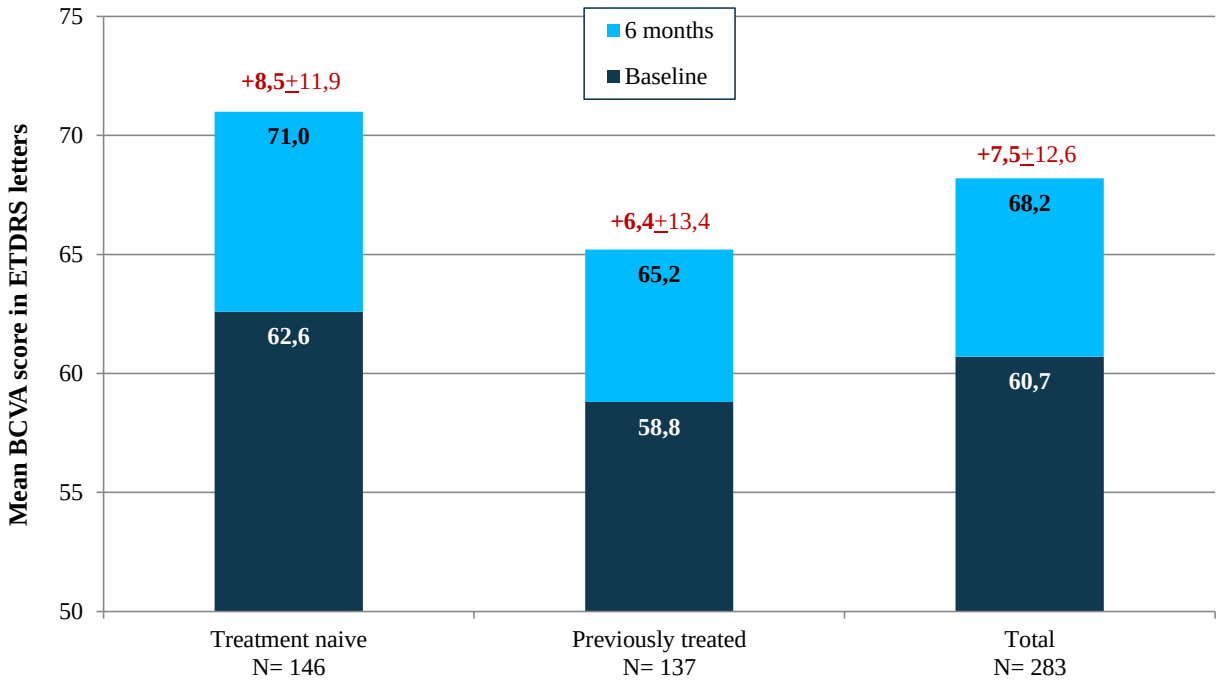
Table 17: Change in BCVA at 6 months, in letter count

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
BCVA at baseline	N	146	137	283
	Mean ± SD	62.6 ± 14.1	58.8 ± 16.7	60.7 ± 15.5
	CI (95%)	[60.3 ; 64.9]	[56.0 ; 61.6]	[58.9 ; 62.5]
	Median	65.0	64.0	65.0
	Q1 ; Q3	54.0 ; 73.0	50.0 ; 69.0	53.0 ; 72.0
	Min ; Max	9 ; 85	0 ; 83	0 ; 85
BCVA at 6 months	N	146	137	283
	Mean ± SD	71.0 ± 12.3	65.2 ± 12.6	68.2 ± 12.8
	CI (95%)	[69.0 ; 73.1]	[63.1 ; 67.3]	[66.7 ; 69.7]
	Median	73.0	67.0	69.0
	Q1 ; Q3	69.0 ; 77.0	58.0 ; 74.0	65.0 ; 76.0
	Min ; Max	8 ; 85	19 ; 85	8 ; 85
Change in BCVA at 6 months	N	146	137	283
	Mean ± SD	8.5 ± 11.9	6.4 ± 13.4	7.5 ± 12.6
	CI (95%)	[6.5 ; 10.4]	[4.2 ; 8.7]	[6.0 ; 9.0]
	Median	8.0	4.0	5.0
	Q1 ; Q3	0.0 ; 14.0	-1.0 ; 12.0	0.0 ; 12.0
	Min ; Max	-45 ; 47	-23 ; 67	-45 ; 67
≤ - 15 letters	N (%)	1 (0.7%)	3 (2.2%)	4 (1.4%)
]-15, - 10] letters	N (%)	2 (1.4%)	5 (3.6%)	7 (2.5%)
]-10, -5] letters	N (%)	7 (4.8%)	12 (8.8%)	19 (6.7%)
]-5, 0[letters	N (%)	16 (11.0%)	16 (11.7%)	32 (11.3%)
[0, 5[letters	N (%)	31 (21.2%)	35 (25.5%)	66 (23.3%)
[5, 10[letters	N (%)	35 (24.0%)	21 (15.3%)	56 (19.8%)
[10, 15[letters	N (%)	18 (12.3%)	18 (13.1%)	36 (12.7%)
≥ 15 letters	N (%)	36 (24.7%)	27 (19.7%)	63 (22.3%)

Reference: Table 4.2.1 in Annex 2: Tables, Figures and Listings

Overall, mean (±SD) change in BCVA at 6 months was +7.5 ± 12.6 letters . Treatment naïve patients had higher improvement in BCVA (+8.5 ± 11.9 letters) compared to previously treated patients (+6.4 ± 13.4 letters), but baseline BCVA was slightly lower in previously treated patients (58.8 vs. 62.6) (see Figure 2).

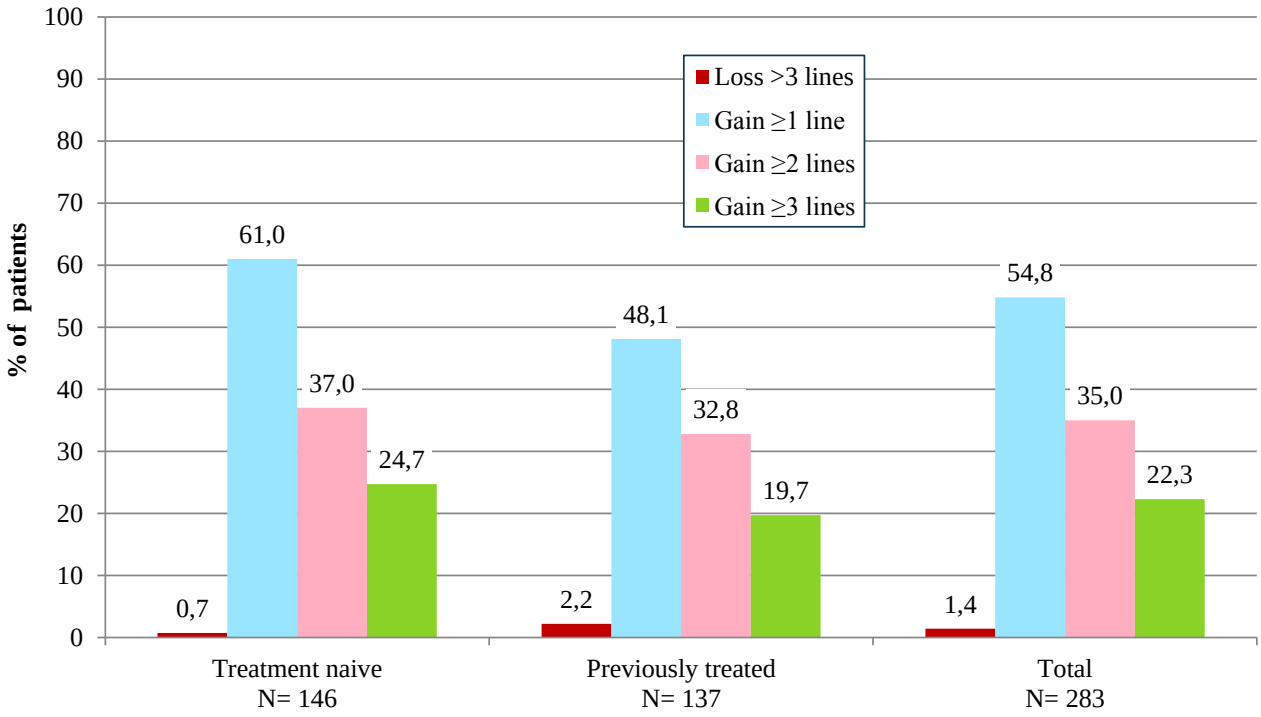
Figure 2: Mean change in BCVA at 6 months



Reference: Table 4.2.1 in Annex 2: Tables, Figures and Listings

More than half of patients (54.8%) achieved an improvement in BCVA of at least 1 line (5 letters) 6 months after the first injection of IVT aflibercept, with 35.0% achieving a gain of at least 2 lines, and 22.3% achieving a gain of at least 3 lines. Results are quite similar in both subgroups (treatment naïve and previously treated patients) (see Figure 3).

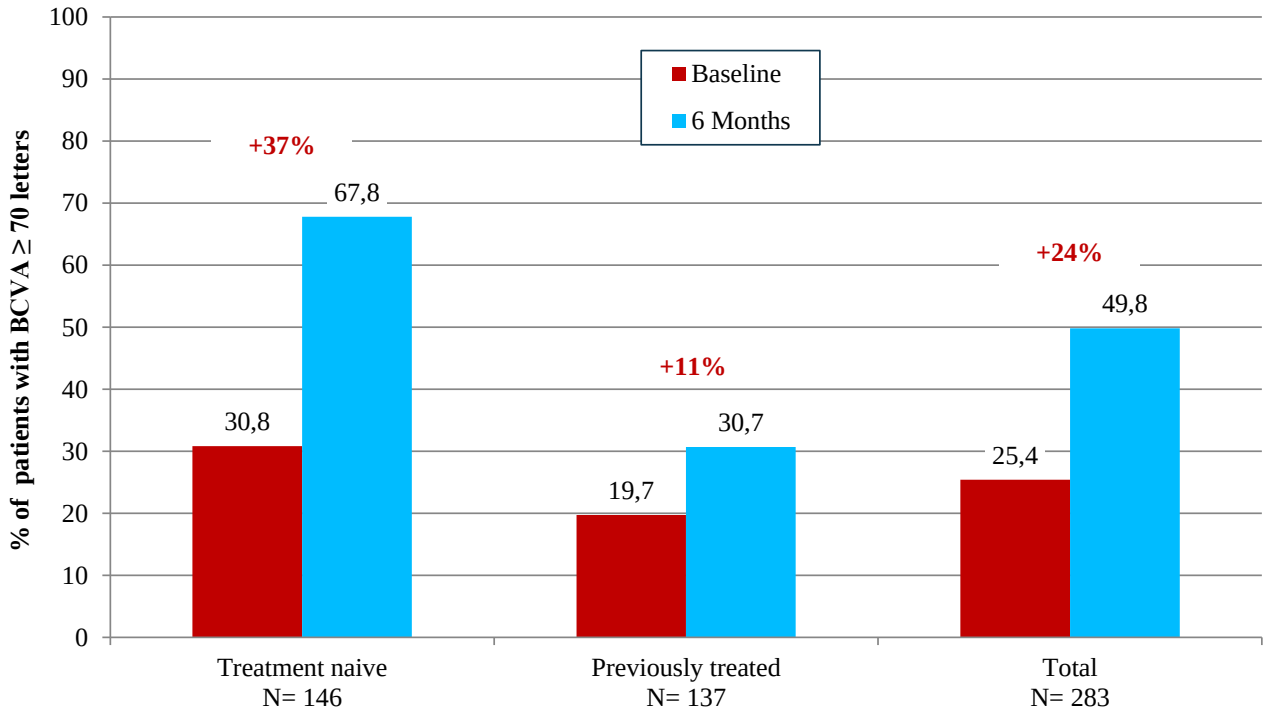
Figure 3: Gain and loss in BCVA at 6 months



One line is equivalent to 5 letters
Reference: Table 4.2.1 in Annex 2: Tables, Figures and Listings

At baseline, respectively 30.8% and 19.7% of treatment naïve and previously treated patients had a BCVA ≥ 70 letters. At 6 months, percentages reached 67.8% in treatment naïve patients and 30.7% in previously treated patients. Overall, the rate of patients achieving BCVA ≥ 70 letters increased by 24.4% 6 months after the first injection of IVT aflibercept (see Figure 4).

Figure 4: BCVA ≥ 70 letters, evolution over 6-months follow-up period



Reference: Tables 2.2.4.1 and 4.2.1 in Annex 2: Tables, Figures and Listings

10.4.1.2 Change in the CRT at 6 months

OCT parameters (CRT and presence of sub-retinal and intra-retinal fluid) at baseline and at 6 months are presented in Annex 2: Tables, Figures and Listings, Tables 5.1.1, 5.1.2, 5.2.1 and 5.2.2.

Results are summarized in Table 18 and Figure 5.

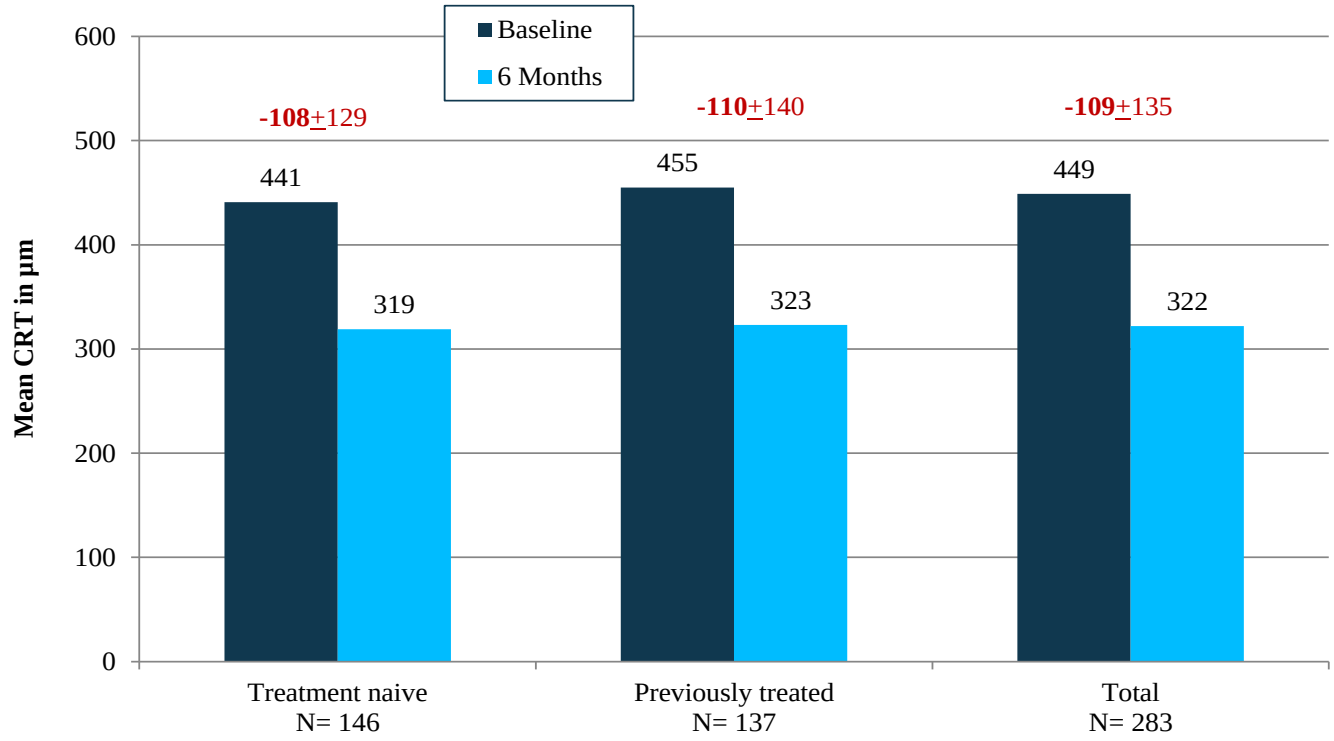
Mean (±SD) CRT at baseline was 449 ± 130 µm and was similar in treatment naïve and previously treated patients. Mean (±SD) change in CRT at 6 months was 109 ± 135 µm. No difference in CRT change was observed in mean change between the 2 subgroups. Median change were respectively -84 and -81 µm in treatment naïve and previously treated patients.

Table 18: Change in CRT at 6 months

		Treatment naïve N = 146	**Previously treated N = 137**	**Total N = 283**
CRT at baseline (µm)	N	138	128	266
	Missing values	5	8	13
	Mean ± SD	444.1 ± 121.1	455.1 ± 139.0	449.4 ± 129.9
	CI (95%)	[423.7 ; 464.5]	[430.8 ; 479.4]	[433.7 ; 465.1
	Median	425.5	424.5	425.5
	Q1 ; Q3	355.0 ; 517.0	352.0 ; 522.5	352.0 ; 519.0
	Min ; Max	229 ; 820	212 ; 980	212 ; 980
CRT at 6 months (µm)	N	51	63	114
	Missing values	95	74	169
	Mean ± SD	319.4 ± 86.6	323.1 ± 97.6	321.5 ± 92.4
	CI (95%)	[295.1 ; 343.8]	[298.5 ; 347.7]	[304.3 ; 338.6]
	Median	297.0	301.0	299.5
	Q1 ; Q3	261.0 ; 377.0	253.0 ; 371.0	257.0 ; 372.0
	Min ; Max	79 ; 588	142 ; 737	79 ; 737
Change in CRT at 6 months (µm)	N	50	62	112
	Missing values	96	75	171
	Mean ± SD	-107.1 ± 129.2	-109.7 ± 139.7	-108.5 ± 134.6
	CI (95%)	[-143.8 ; -70.4]	[-145.2 ; -74.2]	[-133.7 ; -83.3]
	Median	-84.0	-80.5	-84.0
	Q1 ; Q3	-172.0 ; -40.0	-162.0 ; -25.0	-166.0 ; -30.0
	Min ; Max	-444 ; 165	-591 ; 129	-591 ; 165

Reference: Table 5.2.1 in Annex 2: Tables, Figures and Listings

Figure 5: Mean change in CRT at 6 months



Reference: Table 5.2.1 in Annex 2: Tables, Figures and Listings

10.5 Other analyses

10.5.1 DME monitoring

Data related to DME monitoring (type of visits and number of visits) are detailed in Annex 2: Tables, Figures and Listings, Tables 6.1.1, 6.1.2, 6.2.1 and 6.2.2.

Table 19 summarizes the type and the number of visits performed per patients during the first 6-month follow-up period.

Overall, the median number of visits per patient over the 6-month follow-up period was 7 visits while at least 50% of patients did not perform any visit for diabetes during the same period (i.e. median number of visits per patient for diabetes = 0). The median number of monitoring visits per patient (i.e. visits involving only monitoring ophthalmological exams without any injection) was 2 visits. Aside from visits with injection, (median number per patient 5 visits), more than a quarter of patients (26.5%) have performed at least 3 monitoring visits (up to 7) within the first 6 months of treatment. As regards ophthalmological assessments, the median number of visits involving visual acuity evaluation was 3 vs. 2 visits involving OCT measurement.

Table 19: Type and number of visits related to DME monitoring

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
No of visits/patient [a,b]	N	146	137	283
	Mean ± SD	7.0 ± 1.3	6.9 ± 1.6	6.9 ± 1.4
	Median	7.0	7.0	7.0
	Q1 ; Q3	6.0 ; 8.0	6.0 ; 8.0	6.0 ; 8.0
	Min ; Max	4 ; 11	2 ; 12	2 ; 12
2 visits	N (%)	0 (0.0%)	1 (0.7%)	1 (0.4%)
3 visits	N (%)	0 (0.0%)	2 (1.5%)	2 (0.7%)
4 visits	N (%)	4 (2.7%)	4 (2.9%)	8 (2.8%)
5 visits	N (%)	15 (10.3%)	16 (11.7%)	31 (11.0%)
6 visits	N (%)	32 (21.9%)	29 (21.2%)	61 (21.6%)
7 visits	N (%)	47 (32.2%)	47 (34.3%)	94 (33.2%)
8 visits	N (%)	34 (23.3%)	21 (15.3%)	55 (19.4%)
> 8 visits	N (%)	14 (9.6%)	17 (12.4%)	31 (11.0%)
No of visits with injection/patient [a,c]	N	146	137	283
	Mean ± SD	5.3 ± 1.2	4.8 ± 1.3	5.0 ± 1.3
	Median	5.0	5.0	5.0
	Q1 ; Q3	5.0 ; 6.0	4.0 ; 6.0	4.0 ; 6.0
	Min ; Max	1 ; 8	1 ; 8	1 ; 8
1 visit with injection	N (%)	1 (0.7%)	2 (1.5%)	3 (1.1%)
2 visits with injection	N (%)	2 (1.4%)	6 (4.4%)	8 (2.8%)
3 visits with injection	N (%)	12 (8.2%)	17 (12.4%)	29 (10.2%)
4 visits with injection	N (%)	15 (10.3%)	22 (16.1%)	37 (13.1%)
5 visits with injection	N (%)	45 (30.8%)	45 (32.8%)	90 (31.8%)
6 visits with injection	N (%)	58 (39.7%)	39 (28.5%)	97 (34.3%)
> 6 visits with injection	N (%)	13 (8.9%)	6 (4.4%)	19 (6.7%)
No of monitoring visits/patient [a,d]	N	146	137	283
	Mean ± SD	1.7 ± 1.2	2.1 ± 1.5	1.9 ± 1.4
	Median	2.0	2.0	2.0
	Q1 ; Q3	1.0 ; 2.0	1.0 ; 3.0	1.0 ; 3.0
	Min ; Max	0 ; 6	0 ; 7	0 ; 7
0 monitoring visits	N (%)	22 (15.1%)	15 (10.9%)	37 (13.1%)
1 monitoring visit	N (%)	48 (32.9%)	42 (30.7%)	90 (31.8%)
2 monitoring visits	N (%)	46 (31.5%)	35 (25.5%)	81 (28.6%)
3 monitoring visits	N (%)	18 (12.3%)	23 (16.8%)	41 (14.5%)
4 monitoring visits	N (%)	8 (5.5%)	11 (8.0%)	19 (6.7%)
> 4 monitoring visits	N (%)	4 (2.7%)	11 (8.0%)	15 (5.3%)

		Treatment naïve N = 146	Previously treated N = 137	Total N = 283
No of visits with VA assessment/patient [a,e]	N	146	137	283
	Mean ± SD	2.8 ± 1.6	3.0 ± 1.7	2.9 ± 1.6
	Median	2.0	3.0	3.0
	Q1 ; Q3	2.0 ; 4.0	2.0 ; 4.0	2.0 ; 4.0
	Min ; Max	0 ; 6	0 ; 7	0 ; 7
No of visits with OCT assessment/patient [a,e]	N	146	137	283
	Mean ± SD	2.6 ± 1.5	3.0 ± 1.6	2.8 ± 1.5
	Median	2.0	3.0	2.0
	Q1 ; Q3	2.0 ; 3.0	2.0 ; 4.0	2.0 ; 4.0
	Min ; Max	0 ; 6	0 ; 7	0 ; 7
Number of visits for diabetes/patient [f]	N	146	137	283
	Mean ± SD	0.4 ± 0.8	0.7 ± 1.3	0.5 ± 1.1
	Median	0.0	0.0	0.0
	Q1 ; Q3	0.0 ; 0.0	0.0 ; 1.0	0.0 ; 1.0
	Min ; Max	0 ; 5	0 ; 7	0 ; 7

[a] visits related to study eye
[b] visits involving ophthalmological exams (visual acuity assessment and/or OCT and/or FA and/or FP) and/or injection
[c] visits with injection of of EYLEA® in study eye +/- monitoring exams
[d] monitoring visits only performed after the first injection of EYLEA® (i.e. involving visual acuity assessment and/or OCT and/or FA and/or FP)
[e] visits performed after the first injection of EYLEA®
[f] visit to a doctor (either general practitioner or diabetologist) for diabetes management
Reference: Table 6.2.1 in Annex 2: Tables, Figures and Listings

10.6 Adverse events/adverse reactions

All data regarding TEAE are presented in Annex 2: Tables, Figures and Listings, Tables 7.1.1 and 7.1.2, and Listings 7.1.1 and 7.1.2.

Overall summaries of ophthalmological and non-ophthalmological TEAE are presented in Table 20 and Table 21 on the SS. Frequency tables according to SOC/PT classification are not presented in this interim report as only 252 TEAE over the 523 recorded in the eCRF have been yet coded. Frequency of TEAE by SOC/PT would therefore be not representative of the frequency actually observed.

Sixty-six patients (17.1%) experienced at least one ophthalmological TEAE possibly related to EYLEA® treatment, but none of them was serious TEAE. Twenty-eight patients (7.3%) experienced at least one ophthalmological TEAE related to procedure, including one serious TEAE.

For 5 patients, non-serious ophthalmological TEAE led to EYLEA® withdrawal.

Overall, 124 patients (32.1%) experienced 282 non-ophthalmological TEAE, 32 (8.3%) of whom having experienced a serious non-ophthalmological TEAE. Sixty-six patients experienced at least one non-ophthalmological TEAE possibly related to EYLEA® treatment, and TEAE was serious in 2 of them (hemorrhagic stroke and coronary artery stenosis).

Three patients experienced fatal TEAE (myocardial infarction, cardiac decompensation and cardiogenic shock), but none of them was assessed as related to EYLEA® treatment.

Table 20: Overall summary of ophthalmological TEAE

Ophthalmological TEAE		Total N = 386	[No of events]
Any TEAE	N (%) [n]	132 (34.2%)	[241]
Any serious TEAE	N (%) [n]	11 (2.8%)	[12]
Any TEAE related to EYLEA® treatment	N (%) [n]	66 (17.1%)	[114]
Any serious TEAE related to EYLEA® treatment	N (%) [n]	0 (0.0%)	[0]
Any TEAE related to procedure	N (%) [n]	28 (7.3%)	[41]
Any serious TEAE related to procedure	N (%) [n]	1 (0.3%)	[1]
Any TEAE leading to EYLEA® withdrawal	N (%) [n]	5 (1.3%)	[5]
Any serious TEAE leading to EYLEA® withdrawal	N (%) [n]	0 (0.0%)	[0]
Any TEAE leading to death	N (%) [n]	0 (0.0%)	[0]

Reference: Table 7.1.1 in Annex 2: Tables, Figures and Listings

Table 21: Overall summary of non-ophthalmological TEAE

Non-ophthalmological TEAE		Total N = 386	[No of events]
Any TEAE	N (%) [n]	124 (32.1%)	[282]
Any serious TEAE	N (%) [n]	32 (8.3%)	[60]
Any TEAE related to EYLEA® treatment	N (%) [n]	66 (17.1%)	[115]
Any serious TEAE related to EYLEA® treatment	N (%) [n]	2 (0.5%)	[3]
Any TEAE related to procedure	N (%) [n]	10 (2.6%)	[21]
Any serious TEAE related to procedure	N (%) [n]	0 (0.0%)	[0]
Any TEAE leading to EYLEA® withdrawal	N (%) [n]	7 (1.8%)	[7]
Any serious TEAE leading to EYLEA® withdrawal	N (%) [n]	4 (1.0%)	[4]
Any TEAE leading to death	N (%) [n]	3 (0.8%)	[3]

Reference: Table 7.1.2 in Annex 2: Tables, Figures and Listings

11. Discussion

11.1 Key results

The APOLLON study is a prospective, multi-center, observational study in DME patients treated with IVT aflibercept. Although focal/grid laser has been the standard of care for DME for a long time, the role of VEGF in the pathogenesis of DME has led to investigation of anti-VEGF agents in these patients [2]. The efficacy of IVT aflibercept in DME treatment was previously demonstrated in clinical studies, but real word evidence data from French patients are not yet available. The main objectives of this study were to evaluate long-term effectiveness and safety of IVT aflibercept in routine clinical practice in France and also to describe the condition of use of EYLEA® in real-conditions settings.

Two-hundred and eighty-three patients were analyzed through this interim analysis at 6 months, 146 of whom were treatment naïve patients (i.e. patients not previously treated with an anti-VEGF agent, laser or intra-ocular steroids in the study eye, and not previously treated with an anti-VEGF agent or intra-ocular steroids in the other eye) and the 137 remaining were previously treated patients. Patients had mean (±SD) age of 65.6 ± 11.3 years (range, 19-90 years) and most of them were followed for their diabetes for more than 10 years. Median time since DME diagnosis was 1 month in treatment naïve patients vs. 25 months in previously treated patients. Approximately two third of previously treated patients had been previously treated with IVT anti-VEGF (other than aflibercept), which is in accordance with the standards of use. Baseline BCVA and CRT were similar in treatment naïve patients and previously treated patients. Mean (±SD) baseline BCVA was 60.7 ± 15.5 letters, and mean CRT was 449 ± 130 µm.

Over the 6-month follow-up period, patients had a mean (±SD) of 6.9 ± 1.4 visits referring to study eye during which they received a mean (±SD) of 5.3 ± 1.2 injections.

The evolution of BCVA and CRT at 6 months indicate an improvement of visual and anatomic characteristics in both subgroups (treatment naïve and previously treated patients), but improvement in BCVA was more important in treatment naïve patients (median change of +8.0 vs. +4.0 letters in previously treated patients). This important improvement in treatment naïve patients is also illustrated by the proportion of patients who achieved the patient beneficial threshold of 70 letters for BCVA assessment which increased by 37% at 6 months compared to 11% in previously treated patients. As regards CRT results, treatment naïve patients and patients previously treated had similar CRT before the first injection of EYLEA® (i.e. 449.4 ± 129.9 µm) which suggest that previous DME treatment did not significantly improve anatomic parameters while EYLEA® treatment significantly reduced edema in both subgroups (CRT decreased by -108.5 ± 134.6) after 6 months of treatment. These results are promising but long-term efficacy of IVT aflibercept must be confirmed at 12 and 24 months.

Safety results are common to the known safety profile observed in RCT. No new safety event has been identified in this analysis. Among the population, 66 (17.1%) patients experienced adverse event related to EYLEA®, and only 2 patients a serious one.

11.2 Limitations

It is well known that the value of observational studies is a matter of debate [9-11]. Nevertheless, observational studies are useful and necessary to observe the effect of the exposure in real life conditions.

Results for effectiveness variables have to be interpreted carefully because of the uncontrolled setting: time periods between follow-up visits are much more variable than in controlled clinical studies in which a fixed visit schedule has to be maintained. Within this first interim analysis, patients included in the analyses are patients from the FAS who were followed 6 months from the first EYLEA® injection (i.e. with a BCVA evaluation or a CRT evaluation or an EYLEA® injection or a follow-up visit performed within the time frame of [4.5-6.5[months from the first EYLEA® injection). Therefore patients who prematurely discontinued the study before 4.5 months are not considered within the interim analysis at 6 months.

In addition, ophthalmological assessments have been performed according to routine clinical practice in each center. As a consequence, BCVA and CRT were not assessed at each visit and led to some missing data that could limit result interpretation. However, for the purpose of the analysis, missing BCVA values at 6 months were imputed according to 2 imputation methods (median imputation and MCMC imputation, see section 9.9.3).

11.3 Interpretation

Previous studies (including French real world evidence studies) have demonstrated efficacy of IVT anti-VEGF in DME patients with BCVA improvement in treatment naïve patients [4, 12, 13], but none of them has provided real word data for IVT aflibercept. The main results from these studies after 6 months follow-up are summarized in Table 22.

Table 22: Comparison to VIVID study and recent French RWE studies / 6 months follow-up

	APOLLON RWE Treatment naïve patients N = 146	**VIVID** 2Q8 arm Treatment naïve patients N = 135	**ETOILE** RWE Treatment naïve patients N = 104
	aflibercept	aflibercept	ranibizumab
Mean Baseline BCVA (letters)	62.6	58.8	57.9
Mean Final BCVA (letters)	71.0	67.4	64.6
Mean BCVA gain (letters)	+ 8.5	+ 8.5	+6.1
Mean number of injections	5.3	N/A	Not available
Gain ≥ 2 lines (%)	37.0	42.2	Not available
Gain ≥ 3 lines (%)	24.6	19.3	Not available
Final BCVA > 70 letters (%)	67.8	Not available	48.1

Overall, results from APOLLON studies are similar to the previous results published. As such this study adds to the body of evidence from clinical studies. This first interim analysis of APOLLON study provides encouraging results regarding the first 6-month period after the first injection, but further results are needed to confirm efficacy of treatment at 12 and 24 months.

This work also provide a comprehensive picture of conditions of use of EYLEA® in DME patients. Data show that most patients are treated according to the current recommendation, as the mean number of injections received over the first 6-month treatment period is 5.3 ± 1.2, and 72.8% of patients have received at least 5 injections.

11.4 Generalizability

The study was conducted in DME patients and as described in section 10.2.1, baseline characteristics of treatment naïve and previously treated patients reflect that seen in real-conditions settings in US [14]. Moreover, most patient were treated according to the current recommendation, which suggest no major bias as regards treatment administration. Results observed through this interim analysis at 6 months may therefore reflect those observed in DME patients in real-conditions settings.

12. Other information

Not applicable.

13. Conclusion

This first interim analysis of patients treated with IVT aflibercept in real world condition is promising. Treatment with IVT aflibercept resulted in BCVA improvement at 6 months with a mean gain of 8.5 letters for treatment naïve and 6.4 letters for previously treated patients, respectively. Macular edema was also reduced in both subgroups (CRT decrease by 107 µm and 110µm respectively in treatment naïve and previously treatment patients).

No new safety profile has been observed with 17.1% of patients having experienced an EYLEA® related adverse event and 0.5% having experienced a serious EYLEA® related adverse event.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 23: List of stand-alone documents

Document Name	Final version and date (if available)*
18636_List of investigators_final	02 JUL 2018
18636_Steering committee members	02 DEC 2015
18636_CRF_final	Version 6.0 dated 15 MAY 2015
18636_DMP	Version 5.0 dated 24 OCT 2017
18636_SAP	Version 2.0 dated 06 FEB 2018

Annex 2: Tables, Figures and Listings

See Table, Figures and Listing version 3.0 dated 13 JUN 2018.

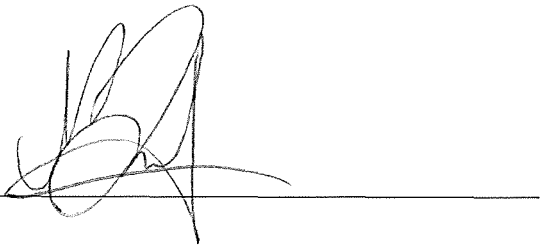
Annex 3: Signature Pages

Signature Page - Country Medical Director

Title	APOLLON — A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept
Report version and date	Version 1.0 – 03 JUL 2018
IMPACT study number	18636
Study type / Study phase	PASS: ☒ YES ☐ NO Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	EUPAS15687
Medicinal product	EYLEA®
Study Initiator and Funder	Bayer Healthcare SAS, 59120 Loos, France

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: *Moncef BOUKERROU*

Date, Signature: 04/07/18, 

Signature Page - OS Conduct Responsible

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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: *Anne Marie DELAUNAY*

Date, Signature: 03-Jul 2018,

Signature Page - OS Medical Expert

Title	APOLLON — A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept
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Study Initiator and Funder	Bayer Healthcare SAS, 59120 Loos, France

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: *Ingrid DUFOUR*

Date, Signature: 04 July 2018 _____

Signature Page - OS Safety Leader

Title	APOLLON — A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept
Report version and date	Version 1.0 – 03 JUL 2018
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EU PAS register number	EUPAS15687
Medicinal product	EYLEA®
Study Initiator and Funder	Bayer Healthcare SAS, 59120 Loos, France

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: *Virginie VERLYCK*

Date, Signature: 23107/18, _____

Signature Page - OS Statistician (ES)

Title	APOLLON — A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept
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Study Initiator and Funder	Bayer Healthcare SAS, 59120 Loos, France

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: *Nathalie JANOT-VERNET*

Date, Signature: 03 JUL 2018 , _____

Signature Page - OS Medical writer (ES)

Title	APOLLON — A prospective observational study conducted in France to describe routine clinical practice for treatment naïve or previously treated patients with diabetic macular edema (DME) who are starting IVT aflibercept
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Medicinal product	EYLEA®
Study Initiator and Funder	Bayer Healthcare SAS, 59120 Loos, France

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: *Lise BOSQUET*

Date, Signature: 03 July 2018, _____