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 intravitreal (IVT) aflibercept
Report version and date	Version 1.0, 06 JUL 2020
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
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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Confidentiality statement:

Table of contents

Table of illustrations

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 intravitreal (IVT) aflibercept.
Report version and date **Author**	Version 1.0, 06 JUL 2020 PPD
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 (phase II), RESTORE (phase III), RISE and RIDE (phase III). The RESTORE trial evaluated ranibizumab treat-to-target PRN (with or without laser) versus laser therapy alone. Visual and anatomical endpoints were significantly more improved in the ranibizumab PRN (ProReNata) groups than in the laser group at 12 months. The RESTORE extension study demonstrated that efficacy results obtained at 12 months could be maintained over 36 months with fewer injections over time. The RISE and RIDE phase III trials evaluated ranibizumab 0.3 and 0.5 mg dosed monthly versus sham with less frequent dosing. Substantial improvements in visual and anatomical outcomes observed at month 24 were sustained through month 36 with regular monthly dosing, and to 5 years with less frequent dosing. Safety differences, in the presence of equivalent efficacy between the two doses, led to the approval of the 0.3-mg dose of ranibizumab for the treatment of DME in the US. The benefits of IVT aflibercept in DME have been established in three key studies, DA VINCI (phase II), VIVID^{DME} and VISTA^{DME} (phase III). The primary objective of the VIVID and VISTA studies was to evaluate the efficacy of IVT aflibercept injections compared with macular laser photocoagulation in improving visual acuity in patients with DME. Eyes were randomized in a 1:1:1 ratio to receive either aflibercept (2 mg) every 4 weeks, or aflibercept (2 mg) every 8 weeks after 5 initial monthly doses (from baseline to week 16) or macular laser photocoagulation. 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. The Diabetic Retinopathy Clinical Research Network (DRCRnet) conducted the study Protocol T. Protocol T is a US-government-sponsored, independent, randomized, three-way head-to-head study which compared for the first time the relative efficacy and safety of IVT aflibercept (2 mg), bevacizumab (1.25 mg) and ranibizumab (0.3 mg) administered in an as needed regimen for the treatment of DME. In the overall study population, the mean ±SD improvement in the BCVA letter score from baseline to 1 year was significantly greater with aflibercept (13.3 ±11.1 letters) than with bevacizumab (9.7 ±10.1 letters; $p<0.001$) or ranibizumab (11.2 ±9.4 letters; $p=0.03$). The median number of injections was 9 with aflibercept and 10 with bevacizumab and ranibizumab. When baseline BCVA was worse than 20/40 (moderate visual impairment; 49% of study eyes), aflibercept demonstrated a significantly greater mean BCVA improvement (18.9 letters) than bevacizumab (11.8 letters) and ranibizumab (14.2 letters). Moreover, in this group, a significantly higher proportion of patients in the aflibercept treatment group showed a ≥15-letter improvement (67%) compared with ranibizumab (50%) and bevacizumab (41%). 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 were to describe outcomes, monitoring and treatment patterns in routine clinical practice in patients with DME, either treatment-naïve 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.
	
	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 primary endpoint was the mean change in BCVA between the initial visit and 12 months.
	
	The secondary objectives and endpoints 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.
	  • The mean change in CRT from baseline at 12 months
	  • The proportion of patients without fluid as measured on OCT at 12 months
	• To describe anatomical and functional changes from baseline through 24-month follow up.
	  • The mean change in BCVA from baseline at 24 months
	  • The mean change in CRT from baseline at 24 months
	  • The proportion of patients without fluid as measured on OCT at 24 months
	  • The proportion of patients with change in FA and FP parameters
	• To describe the evolution of HbA1c level and blood pressure throughout 24 months (when observed).
	  • The mean change in HbA1c level from baseline at 24 months

	• The mean change in blood pressure from baseline at 24 months • To describe DME monitoring in patients receiving IVT aflibercept in routine clinical practice. • The number of follow-up visits with monitoring only (e.g diagnostic purposes, monitoring of adverse events / safety) over 12 and 24-month follow-up periods • The number of follow-up visits combining monitoring and injection over 12 and 24-month follow-up periods • The number of monitoring visits for diabetes (by diabetologists, general practitioners) outside the study center over 12 and 24-month follow-up periods • The number of OCT assessments over 12 and 24-month follow-up periods • The number of FP assessments over 12 and 24-month follow-up periods • The number of FA assessments over 12 and 24-month follow-up periods • The number of VA measurements over 12 and 24-month follow-up periods • To describe the regimen with IVT aflibercept from initial visit to 24-month follow-up visit. • The reason for starting IVT aflibercept (based on VA, OCT, both, other) • The number of IVT aflibercept injections received over 12 and 24-month follow-up periods • Time between IVT aflibercept injections • Type and frequency of adjunctive therapy used for DME (i.e. surgery, focal laser, steroids) • Reason for retreatment (based on VA, OCT or other findings) • To describe the adverse events occurred during the study.

	• Frequency and severity of ocular and non-ocular adverse events • To describe previous treatments for DME (in previously treated patients only). • Type of treatment, duration, time since last treatment
Study design	This study was 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 was initiated between Q3 2016 and Q3 2017. Patients should be followed up for 24 months or until it was no longer feasible (e.g. lost to follow-up, withdrawal, death, and transfer to another physician), whichever was 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 reported in 2015 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 is the change in BCVA between the initial visit and 12 months.
	The secondary variables are:
	• Mean change in BCVA between baseline and 12-month follow-up for the entire study population
	• Mean change in BCVA between baseline and 24-month follow-up for all groups
	• Mean change in CRT between baseline and 12-month follow-up for all groups
	• Mean change in CRT between baseline and 24-month follow-up for all groups
	• Proportion of patients with no fluid determined by OCT at baseline, 12-month and 24-month follow-up
	• Proportion of patients with presence of any of these parameters at baseline and month 24 for the treatment naïve group, the previously treated group and the entire study population, if evaluated
	  • Micro-aneurysms and haemorrhages
	  • Neovascularization of the disc
	  • New vessels elsewhere than the disc
	  • capillary leakage
	  • Area of fluorescein leakage due to new vessels
	  • Hard exudates

	• Soft exudates (cotton wool patches) • Micro-aneurysms and haemorrhages • Intra retinal micro vascular abnormalities • Neovascularization of the disc • New vessels • Change in HbA1c level and blood pressure during the 24-months DME monitoring for patients receiving IVT aflibercept: • History of DME monitoring • Number of monitoring only visits (e.g diagnostic purposes, monitoring of adverse events / safety) over 12 and 24 months • Number of of visits combining monitoring and injection over 12 and 24 months • Number of monitoring visits for diabetes (by diabetologists, general practitioners) outside the study centre over 12 and 24 months (if known by the ophthalmologist) • Number of optical coherence tomography (OCT) assessments over 12 and 24 months. • Number of fundus photography assessments over 12 and 24 months • Number of of Fluorescein angiography (FA) assessments over 12 and 24 months • Number of visual acuity measurements over 12 and 24 months • IVT aflibercept regimen • Reason for initiating IVT aflibercept (based on VA, OCT, both, other) • Proportion of patients with bilateral treatment • Number of treatment / injection visits over 12 and 24 months • Mean, minimal and maximum interval (days) between injections • Type and frequency of adjunctive therapy post IVT aflibercept initiation (ie, surgery, focal laser, steroids, etc.)

	• In previously treated patients, type, duration (months) of the previous treatment(s) and date of the last administered treatment. • Frequency and severity of ocular and non-ocular adverse events 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. The data were entered by the treating ophthalmologist in the clinical database (eCRF). BCVA results, OCT results (CRT and presence of fluid), results of FA and FP exams were recorded at the initial visit before the first injection of IVT aflibercept and at each follow-up visit, if available. If the ophthalmologist reported a BCVA value with another scale than the ETDRS, this information was then converted into the right scale. 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. Information to be documented on IVT aflibercept included the dates of injection, injection volume administered and the injected eye. HbA1c values and blood pressure were collected at each visit if part of routine assessment by the ophthalmologist. Ocular and non-ocular safety events were recorded.
Results	From 15 SEP 2016 to 05 JUL 2017, 56 ophthalmologists participated in the study and contributed 402 patients, 377 (93.8%) of whom are included in the FAS. Out of these, 206 (54.6%) patients were treatment-naïve patients and 171 (45.4%) were previously treated patients. Overall 542 eyes were injected with IVT aflibercept within the study observational period and 165 (43.8%) patients received bilateral injections. For the purpose of the analysis, the eye with the worst visual acuity at baseline was considered as the study eye. Patients had mean (±SD) age of 65.9 (±11.1) years (range, 19-91 years) and were slightly more male (55.7%). Less than 10% of patients were current smokers and 28.7% were former smokers. Mean (±SD) body mass index was 29.1 (±5.8) kg/m² and mean (±SD) blood pressure was 142 (±19) / 78 (±12) mmHg. Globally, demographic data did not significantly differ between treatment-naïve and previously treated patients.

	Approximately three quarter of the patients (74.0%) suffered from hypertension and one third (34.8%) had cardiovascular disease history. Few patients had stroke history (5.2%) or transient ischemic attack history (2.0%). Overall, 40.4% of the patients had experienced at least one previous ophthalmological surgery, mainly (36.8%) cataract surgery, which was more common in patients previously treated for DME (46.4% vs. 28.5% in treatment-naïve patients). Mean (±SD) time since diabetes diagnosis was 17.5 (±12.2) years for treatment-naïve patients and 19.3 (±11.4) years for previously treated patients. Mean (±SD) glycemia was 13.0 (±15.6) mmol/L and 8.4 (±8.1) mmol/L, respectively. Mean (±SD) HbA1c level was 7.7 (±1.4) % and did not significantly differ in treatment-naïve and previously treated patients. Mean (±SD) time since DME diagnosis for study eye was 7.1 (±17.8) months in treatment-naïve patients and 39.0 (±38.8) in previously treated patients. Median times were 1.2 month and 28.6 months, respectively. Among previously treated patients, 66.5% had been previously treated with IVT anti-VEGF agents in the study eye (mainly with ranibizumab), 64.8% of patients had been previously treated with photocoagulation laser (mainly pan-photocoagulation laser) and 27.3% of patients had been previously injected with intraocular steroids. Almost all treatment-naïve patients (94.7%) started IVT aflibercept treatment because of a decrease of visual acuity due to DME. For previously treated patients, the main reason for starting IVT aflibercept treatment was the insufficient efficacy of previous DME treatments (78.2%). The mean (±SD) number of injections received per patient over the 6-, 12 and 24-month observational periods were 4.9 (±1.4), 7.3 (±2.6) and 11.6 (±4.8) injections, respectively and no difference was observed between treatment-naïve and previously treated patients. During the study, 27.9% of the patients discontinued IVT aflibercept permanently, mainly to switch to another treatment (13.8%). Dexamethasone (IVT implant) was the most common treatment prescribed (9.5%). A large majority of patients (91.5%) received at least one concomitant medication during the observational study period, mainly non-ophthalmological medication (88.1%). The most common medications used were drugs used in diabetes (85.7%), agents acting on the renin-angiotensin system (53.1%), lipid modifying agents (45.4%) and analgesics (38.5%). Approximately one third of patients (31.3%) received a concomitant ophthalmological medication in the study eye, mainly anti-infectives (8.0%), beta blocking agents (6.6%),

	non-steroidal anti-inflammatory agents (5.8%) and sympathomimetics in glaucoma therapy (5.3%). Overall, 66 (17.5%) patients experienced at least one concomitant ophthalmological surgery in the study eye within the study observational period, mainly cataract surgery (12.5%). Sixty-nine (18.3%) patients have received at least one adjunctive therapy during the study observational period, mainly laser therapy (64 patients; 17%). Change in BCVA For treatment-naïve patients, mean BCVA was significantly improved at 6, 12 and 24 months from baseline ($p<0.001$). At 12 months, mean (±SD) BCVA score was 70.4 (±14.6) letters and median score reached 73 letters. Mean (±SD) changes in BCVA was +8.2 (±12.1), 46.5% have gained at least 2 lines (i.e. +10 letters or more) and 30.7% have gained at least 3 lines (i.e. +15 letters or more). For previously treated patients, mean BCVA was significantly improved at 6 and 12 months from baseline ($p<0.001$) but 24-month BCVA was not statistically different from baseline ($p=0.41$). At 12 months, mean (±SD) BCVA score was 64.3 (±17.9) letters and median score reached 69 letters. Mean (±SD) changes in BCVA was +4.7 (±11.0) letters, 29.0% have gained at least 2 lines and 16.1% have gained at least 3 lines. The threshold of 70 letters was achieved in 49.8% of the patients (+23.8% from baseline) as early as 6 months. At month 12 and 24, respectively 56.2% and 50.9% of patients achieved BCVA score ≥70 letters. Overall, results were better in treatment-naïve patients compared to previously treated patients. At 12 months, the sensitivity analysis using the missing data imputation via the MCMC method produced similar results to those of the main analysis. Change in OCT parameters Mean CRT has significantly decreased at 6, 12 and 24 months from baseline. At 12 months, mean (±SD) change in CRT was -124.0 (±149.7) µm. The percentage of patients with visible intra-retinal fluid on OCT dropped from 96.1% at baseline to 75.4%, 69.3% and 68.8%, respectively at 6,12 and 24 months. For sub-retinal fluid, the proportion of patients with sub-retinal fluid visible on OCT dropped from 27.7% at baseline to 8.7%, 5.3% and 6.2%, respectively at 6, 12 and 24 months. No difference was observed between treatment-naïve and previously treated patients. The sensitivity analysis using the

	missing data imputation via the MCMC method produced similar results to those of the main analysis. DME monitoring The mean (±SD) number of follow-up visits per patient over the 6-, 12- and 24-month follow-up periods were 6.7 (±1.6), 11.4 (±3.0) and 19.8 (±5.3), respectively. No difference was observed between treatment-naïve and previously treated patients. Change in FA/FP parameters The number of available FA/FP assessments at 24 months is too small and does therefore not allow any relevant analysis. Change in glycaemia and HbA1c level In regards to glycaemia, very few data were routinely collected during the follow-up period, and thus did not allow any relevant analysis on the available data. The results did not show any significant change HbA1c level overtime. Change in blood pressure The results did not show any significant change in blood pressure overtime. Safety Three-hundred and eighty-nine patients recorded 1917 TEAEs within the study period. In regards to the ocular TEAEs, 252 (64.8%) patients experienced 954 ocular TEAEs. Out of them, 53 (13.6%) patients experienced 111 ocular TEAEs related to procedure, mainly (109 TEAEs, 98.2%) non serious TEAEs, 19 (4.9%) patients experienced 21 treatment-related ocular TEAEs (excluding off-label use TEAEs), mainly (19 TEAEs, 90.5%) non serious treatment-related TEAEs and 5 (1.3%) patients experienced 5 non-serious ocular TEAEs that led to treatment discontinuation. Overall, 14 (3.6%) patients experienced 18 serious ocular TEAEs, out of which 2 (11.1%) were related to procedure, 2 (11.1%) were related to treatment and 14 (77.8%) were unrelated to procedure or treatment. The most frequently reported ocular TEAEs was cataract (33 patients, 8.5%). Most ocular TEAEs were reported with a PT incidence ≤2%. In regards to the non-ocular TEAEs, 214 (55.0%) patients experienced 963 non-ocular TEAEs. Out of them, 15 (3.9%) patients experienced 58 non serious TEAEs related to procedure, 7 (1.8%) patients experienced 8 treatment-related TEAEs, mainly (6 TEAEs, 75.0%) non serious treatment-

	related TEAEs and 4 (1.0%) patients experienced 4 TEAEs that led to treatment discontinuation, mainly (3 TEAEs, 75%) non serious TEAEs. Overall, 70 (18.0%) patients experienced 193 serious non-ocular TEAEs out of which 2 (1.0%) were related to treatment, none was related to procedure and 191 (99.0%) were unrelated to procedure or treatment. The most frequently reported non-ocular TEAEs were bronchitis (9 patients, 2.3%) and hypertension (8 patients, 2.1%). Most non-ocular TEAEs were reported with a PT incidence ≤2%. Serious TEAE occurred in 21.6% of the patients. The most frequently reported serious AEs belong to cardiac disorders SOC (20 patients, 5.1%) and surgical and medical procedures (15 patients, 3.9% overall). All other SOC occurred at an incidence <5% and no individual serious TEAE occurred with a PT incidence >1.4%. Eight (2.1%) patients died during the study, but none of TEAEs leading to death was related to the study drug or IVT injection procedure. The most frequently reported treatment-related AEs belong to eye disorders SOC (11 patients, 2.8%, 13 TEAEs). All other SOC occurred at an incidence <2.0% and no individual treatment-related TEAE occurred with a PT incidence >1.7%. Three patients (all previously treated) experienced a serious treatment-related TEAE during the course of the study. Overall, 73 (18.8%) patients experienced 105 TEAEs requiring special attention (as defined in risk management plan). The most frequently reported TEAEs belong to the eye disorders SOC (79 TEAEs, mainly cataract). No safety signal was detected from these special situations.
Discussion	The evolution of BCVA and CRT over the first 1-year follow-up indicates an improvement of visual and anatomic characteristics in both subgroups (treatment-naïve and previously treated patients), but improvement in BCVA was greater in treatment-naïve patients (median change of +8.0 letters vs. +5.0 in previously treated patients). This important improvement in treatment-naïve patients at 12 months is also illustrated by the proportion of patients who achieved the patient beneficial threshold of ≥70 letters for BCVA assessment which increased by 35% compared to 24% in previously treated patients. Additionally, the rate of 31% of treatment-patients who obtained a gain of at least 3 lines (i.e. ≥+15 letters) is also indicative of the very good results observed in these subjects (vs. 16% among previously treated patients). Treatment-naïve

	and previously treated patients had similar CRT before the first IVT aflibercept injection (i.e. 446.6 ±128.6 µm) which suggest that previous DME treatment did not significantly improve anatomic parameters while IVT aflibercept treatment significantly reduced edema in both subgroups (CRT decreased by -124.0 ±149.7 µm from baseline overall). In addition, the significant reduction in the rate of patients with intra and sub-retinal fluid visible at OCT (-25% and -20% from baseline, respectively) attests to the impact of treatment on anatomical parameters. The sensitivity analysis using multiple imputation method produced identical results to the main analysis and thus confirm the validity of the results observed on the full analysis set. These results are also confirmed at 24 months with a long term improvement of BCVA (median change of +7.5 letters and +6.5 letters, respectively in treatment-naïve and previously treated patients) and CRT (CRT decreased by -131.6 ±141.9 µm from baseline overall). Safety results are common to the known safety profile observed in RCT. No new safety event has been identified in this analysis. Among the study population, 26 (6.7%) patients experienced adverse event possibly related to EYLEA®, and only 3 patients a serious one. 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 work also provide a comprehensive picture of conditions of use of EYLEA® in DME patients. In conclusion, the APOLLON study showed that IVT aflibercept was associated with visual and anatomical improvements in patients with DME in routine clinical practice in France. Treatment with IVT aflibercept resulted in a long term BCVA improvement with a mean gain at 12 months of 8.2 letters for treatment-naïve and 4.7 letters for previously treated patients, respectively. The 70 letters threshold was reached by 56% of the patients, and 24% achieved a gain of at least 3 lines overall. Macular edema was also reduced in both subgroups (CRT decrease by 124 µm or overall). 24-month results also confirm the positive impact of IVT aflibercept in DME patients, especially in treatment-naïve patients. The APOLLON study also highlights the good DME management in routine clinical practice in France with a mean number of 4.9 IVT aflibercept injections over the first 6 months and 7.3 injections over the first 12 months. Patients were mainly followed on a monthly basis and injection scheme was compliant with the current recommendations (i.e. loading dose to be injected during the

	first 6 months of treatment). No new safety profile has been observed with 6.7% of patients having experienced an EYLEA® related adverse event and 0.8% having experienced a serious EYLEA® related adverse event. Overall, efficacy and safety results observed in the APOLLON study are consistent with those reported in randomized studies of patients with DME.
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 Annex 1: List of stand-alone documentswhich is available upon request.

2. List of abbreviations

AE	Adverse Event
AFL	Aflibercept
AG	Aktiengesellschaft (Corporation)
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRT	Central Retinal Thickness
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DME	Diabetic Macular Edema
DMP	Data Management Plan
DRCRN	Diabetic Retinopathy Clinical Research Network
EDC	Electronic Data Capture
EDTRS	Early Treatment Diabetic Retinopathy Study
EMA	European Medicine Agency
EU	European Union
ES	External Supplier
FA	Flurorescein Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Fundus Photography
HAS	Haute Autorité de Santé (French Health Authority)
HbA1c	Glycated Hemoglobin
IEC	Independent Ethics Committee
ILM	Internal Limiting Membrane
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRF	Intra-Retinal Fluid
IRMA	Intra-Retinal Microvascular Abnormalities
IVT	Intravitreal
LOCF	Last Observation Carried Forward
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo

MRP	Medical Review Plan
OCT	Optical Computed Tomography
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QRP	Quality Review Plan
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SRF	Sub-Retinal Fluid
TEAE	Treatment-Emergent Adverse Events
TIA	Transient Ischemic Attack
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

3. Investigators

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

4. Other responsible parties

Information on the Steering Committee Members is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

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	12 AUG 2019	
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 report baseline data		14-SEP-2017	Only TFLs, no OS report
Interim report 6 months follow-up		03 JUL 2018	OS Report, sent to HAS
Interim report 12 months follow-up		28 SEP 2018	TFLs only, no OS Report
Database Clean		06 DEC 2019	
Final report of study results		07 JUL 2020	
A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1: List of stand-alone documents which is available upon request. EU, European union; HAS, French Health Authority; IEC, independent ethics committee; IRB, institutional rewiew board: OS, observational study; PAS, post-authorization study; TFL, tables figures and listings.			

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 (phase II), RESTORE (phase III), RISE and RIDE (phase III). The RESTORE trial evaluated ranibizumab treat-to-target PRN (with or without laser) versus laser therapy alone. Visual and anatomical endpoints were significantly more improved in the ranibizumab PRN (ProReNata) groups than in the laser group at 12 months. The RESTORE extension study demonstrated that efficacy results obtained at 12 months could be maintained over 36 months with fewer injections over time. The RISE and RIDE phase III trials evaluated ranibizumab 0.3 and 0.5 mg dosed monthly versus sham with less frequent dosing. Substantial improvements in visual and anatomical outcomes observed at month 24 were sustained through month 36 with regular monthly dosing, and to 5 years with less frequent dosing. Safety differences, in the presence of equivalent efficacy between the two doses, led to the approval of the 0.3-mg dose of ranibizumab for the treatment of DME in the US.

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 conducted in 872 patients with DME. Eyes were randomized in a 1:1:1 ratio to receive either IVT aflibercept 2 mg every 4 weeks (2q4), or IVT aflibercept 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation. At week 52, week 100 and week 148, 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).

The Diabetic Retinopathy Clinical Research Network (DRCRN) conducted the study Protocol T (6), a US-government-sponsored, independent, randomized, three-way head-to-head study which compared for the first time and the relative efficacy and safety of intravitreal aflibercept (2 mg), bevacizumab (1.25 mg), and ranibizumab (0.3 mg) in the treatment of DME. In the overall study population, the mean ±SD improvement in the BCVA letter score from baseline to 1 year was significantly greater with aflibercept (13.3 ±11.1 letters) than with bevacizumab (9.7 ±10.1 letters; $p<0.001$) or ranibizumab (11.2 ±9.4 letters; $p=0.03$). The median number of injections was 9 with aflibercept and 10 with bevacizumab and ranibizumab. When baseline BCVA was worse than 20/40 (moderate visual impairment; 49% of study eyes), aflibercept demonstrated a significantly greater mean BCVA improvement (18.9 letters) than bevacizumab (11.8 letters) and ranibizumab (14.2 letters). Moreover, in this group, a significantly higher proportion of patients in the aflibercept treatment group showed a ≥15-letter improvement (67%) compared with ranibizumab (50%) and bevacizumab (41%) (i.e. 63% more aflibercept-treated eyes than bevacizumab-treated eyes [$p<0.001$] and 34% more aflibercept-treated eyes than ranibizumab-treated eyes [$p=0.008$]). At the 1-year visit, in the overall study population, 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). All three treatments were well tolerated without significant differences between groups.

IVT aflibercept was approved for use in DME by the European Medical Agency (EMA) and Food and Drug Administration (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 the French Health Authority (HAS) 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 marketing authorization holder (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 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).

7.1 Primary objective and endpoints

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.

The primary endpoint was the mean change in BCVA from baseline at 12-month follow-up visit.

The primary objective was evaluated separately in the treatment naïve patients and in the previously treated patients.

7.2 Secondary objectives and endpoints

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
    - The mean change in CRT from baseline at 12 months
    - The proportion of patients without fluid as measured on OCT at 12 months
- To describe anatomical and functional changes from baseline through 24-month follow up
    - The mean change in BCVA from baseline at 24 months
    - The mean change in CRT from baseline at 24 months
    - The proportion of patients without fluid as measured on OCT at 24 months
    - The proportion of patients with change in FA and FP parameters
- To describe the evolution of HbA1c level and blood pressure throughout 24 months (when observed)
    - The mean change in HbA1c level from baseline at 24 months
    - The mean change in blood pressure from baseline at 24 months
- To describe DME monitoring in patients receiving IVT aflibercept in routine clinical practice
    - The number of follow-up visits with monitoring only (e.g diagnostic purposes, monitoring of adverse events / safety) over 12 and 24-month follow-up periods
    - The number of follow-up visits combining monitoring and injection over 12 and 24-month follow-up periods

- The number of monitoring visits for diabetes (by diabetologists, general practitioners) outside the study center over 12 and 24-month follow-up periods
- The number of OCT assessments over 12 and 24-month follow-up periods
- The number of FP assessments over 12 and 24-month follow-up periods
- The number of FA assessments over 12 and 24-month follow-up periods
- The number of VA measurements over 12 and 24-month follow-up periods

- To describe the regimen with IVT aflibercept from initial visit to 24-month follow-up visit
  - The reason for starting IVT aflibercept (based on VA, OCT, both, other)
  - The number of IVT aflibercept injections received over 12 and 24-month follow-up periods
  - Time between IVT aflibercept injections
  - Type and frequency of adjunctive therapy used for DME (i.e. surgery, focal laser, steroids)
  - Reason for retreatment (based on VA, OCT or other findings)
- To describe the adverse events occurred during the study
  - Frequency and severity of ocular and non-ocular adverse events
- To describe previous treatments for DME (in previously treated patients only)
  - Type of treatment, duration, time since last treatment

8. Amendments and updates

The study protocol was amended on 13 JAN 2017. The amended protocol is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

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

Table 2: Overview of amendments

No.	Date	Section of study protocol	Amendment / Update	Reason
1	13 JAN 2017	Page 1	Update of EU PAS register number	
1	13 JAN 2017	Page 1	Change of study initiator and funder: Bayer Healthcare AG is replaced by Bayer Healthcare SAS	
1	13 JAN 2017	Pages 7-8	Update of Responsible Parties	
1	13 JAN 2017	Page 16	Update of milestones of the study	Change in timelines
1	13 JAN 2017	Pages 1, 11, 18	Change of wording in main objectives: Replacement of effectiveness by outcomes.	
1	13 JAN 2017	Pages 15, 22	Addition of detail on previous treatments to be considered for analysis sets definition	Lack of details regarding analysis sets definition
1	13 JAN 2017	Pages 11-12, 19-20	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).	Modifications of the primary and secondary objectives in order to calculate mean change from the first IVT aflibercept injection instead from inclusion
1			Disappearance of fluid on OCT is replaced by Proportion of patients without fluid as measured on OCT at	Insufficiently detailed description of the secondary

			baseline, at month 12 and at month 24	objective related to fluid measurement on OCT
1			To describe previous treatments for DME is replaced by To describe type and duration of previous treatments for DME	Insufficiently detailed description of previous DME treatments
1	13 JAN 2017	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	Modification of the study endpoint to match with study objective modification
1	13 JAN 2017	Whole protocol	Change of wording in the whole protocol: “starting IVT aflibercept” is replaced by “initiating IVT aflibercept”	
1	13 JAN 2017	Page 22	Eligibility: addition of details on eligibility criteria: for patient receiving bilateral treatment, the eye with the worst visual acuity at baseline will be considered as the study eye.	Clarification to be provided for patients receiving bilateral treatment with IVT aflibercept
1	13 JAN 2017	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)	Modification of inclusion criteria
1	13 JAN 2017	Pages 25, 26, 27	Hard exudates and soft exudates (cotton wool patches) are measured by fundus photography instead of fluorescein angiography.	Modification of anatomical parameters to be collected according to the technique of imagery

1	13 JAN 2017	Page 27	Additional data collected: reason for end of observation in case of switch from IVT aflibercept treatment to another type of treatment	Reason for switch from IVT aflibercept to another treatment during follow-up, to be collected
1	13 JAN 2017	Page 33	In imaging system paragraph, deletion of centralized reading.	No centralized reading planned in the protocol
BCVA, best-corrected visual acuity; DME, diabetic macular edema; HAS, French Health Authority; IVT, intravitreal; OCT, optical computed tomography; VA, visual acuity.				

9. Research methods

9.1 Study design

9.1.1 Overall study description

This study was a prospective, multi-center, observational study conducted in ophthalmological public or private hospitals or in private practitioners in France. It was planned to include approximately 400 patients initiating IVT aflibercept for DME. 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 IVT aflibercept regimen used in routine clinical practice (including time and number of injections, and adjunctive treatments)

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 without interference by a sponsor or a study protocol.

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.

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.

9.1.2 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 (CRF). 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.

9.1.3 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.

9.1.4 Representativeness

The patients documented in this study were selected only based on eligibility according to inclusion and exclusion criteria as outlined in Section 9.3. No further selection criteria were applied. The study population is representative of the French DME patients followed in all types of ophthalmology centers (public or private hospitals, private practitioners) in real-life conditions.

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 visual acuity loss due to DME - in accordance with the local summary of product characteristics (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 data were collected for each consecutive patient who initiated IVT aflibercept between SEP 2016 and JUL 2017. Patients were followed for 24 months or until it was no longer feasible (e.g. lost to follow-up, withdrawal, death, and transfer to another physician), whichever was earlier.

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 electronic case report form (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.

Three types of visits were defined:

- 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 had 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, regardless of whether or not an injection or any other treatment was given or the disease was only monitored related to diabetic macular edema or diabetic retinopathy.

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 ended with the end of the safety follow-up (i.e. last IVT aflibercept +30 days) or with the patient reaching the maximum observation period of 24 months whichever condition was fulfilled earlier. Switch from IVT aflibercept treatment to another type of treatment was a reason for 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 IVT aflibercept injection.

9.3 Subjects

The study population consists of patients with DME 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: 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: 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; a patient who has been previously treated with anti-VEGF agent, IVT steroid injection or steroid implant in the fellow eye is also considered as previously treated patients.

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

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

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.

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 eCRF. The CRF is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

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	✓	✓	✓
Eligibility	✓		
Patient information and consent	✓		
Demography and clinical characteristics	✓		
Medical & Medication History	✓		
Co-morbidities	✓		
Prior and concomitant medications	✓	✓	✓
Visual Acuity (BCVA)	✓	✓	✓
OCT anatomical measurements	✓	✓	✓
FA anatomical measurements	✓	✓	✓
FP anatomical measurements	✓	✓	✓
Type of visit (monitoring, injection, combined) [a]		✓	
Concomitant treatment for diabetes and adjunctive DME therapy	✓	✓	✓
IVT-AFL injections [b]	✓	✓	✓
Ocular and non-ocular adverse events	✓	✓	✓ [c]
Reasons for discontinuation of observation			✓

[a] only for visits involving study eye.
[b] including reason for injections, i.e. retreatment criteria
[c] patients could continue their treatment beyond the study period; collection of AE had to continue up to 30 days after end of IVT-AFL treatment or until 24 months whichever was earlier.
AE, adverse event; BCVA, best-corrected visual acuity; DME, diabetic macular edema; FA, fluorescein angiography; FP, fundus photography; OCT, optical computed tomography; IVT-AFL, intravitreal aflibercept

9.4.1 Ophthalmological assessments

BCVA, OCT results (CRT and presence of fluid), results of FA and FP exams were recorded at the initial visit before the first injection of IVT aflibercept and at each follow-up visit, if available. 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 Comorbidities

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 section Medical History / Concomitant Diseases. 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 treatments 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 should have 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) also had to be documented. 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 international nonproprietary name (INN), start date, stop date/ongoing, dose, unit, frequency, administration route, indication, and if applicable, the eye(s) treated.

9.4.6 Treatment exposure

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 (i.e. in the 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 injection of IVT aflibercept after enrollment into the study, all non-serious AE had to be documented on the AE Report Form or in the CRF / electronic data capture (EDC) system and forwarded to the MAH within 7 calendar days of awareness. All SAEs 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 Standard Operating Procedures (SOP). 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 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.

Findings generated from prospective observational studies are inevitably subject to biases inherent to study design. Particularly, 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.

The uncontrolled setting may have led to heterogeneity in time period between follow-up visits compared to controlled clinical studies in which a fixed visit schedule is maintained. However, time windows have been defined in the statistical analysis plan to limit bias in statistical analyses.

Another 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. Moreover, monitoring and quality reviews have been performed during the study in order to reduce the number of missing data.

9.7 Study size

The Diabetic Retinopathy Clinical Research Network reported in 2015 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 Main statistical methods9.9.2.

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 Intravitreal injection 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 IVT aflibercept 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).

9.9 Statistical methods

9.9.1 Main summary measures

9.9.1.1 General principle

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 (CI) 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.

- Follow-up data

Efficacy data collected after switch to another DME treatment, i.e. after first administration of dexamethasone (Ozurdex®), ranibizumab (Lucentis®), bevacizumab (Avastin®), triamcinolone (Kenacort®) treatments or vitrectomy, or after date of end of study due to switch to another DME treatment, were not considered in the statistical analyses. Only safety data collected within 30 days after switch to another DME treatment will be considered in the statistical analyses.

- Time windows

For each efficacy endpoint evaluation (e.g. BCVA, CRT), the time between the evaluation and the first IVT aflibercept injection in the study eye will be computed in months as follows:

$$Time\ in\ months = \frac{(Evaluation\ date - First\ Eylea®\ injection\ date)}{30.4375}$$

Time windows have been defined according to the following rules:

Timepoint	**Time window**
1 month	[0.5;1.5[months
2 months	[1.5;2.5[months
3 months	[2.5;3.5[months
4 months	[3.5;4.5[months
6 months	[4.5;6.5[months
12 months	[11;13] months
24 months	[23;25] months

If two evaluations of a parameter were performed within the same time window, the closest evaluation to the theoretical endpoint evaluation date was considered for the efficacy endpoints. This theoretical date was computed based on:

$$Theoretical\ endpoint\ evluation\ date\ at\ M\ months = First\ treatment\ injection\ date + M \times 30.4375$$

Furthermore, if two evaluations linked to the same timepoint were measured at the same distance from the theoretical timepoint, the first evaluation (before the theoretical 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 PPD SOPs.

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 available 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 available at 12 months in the study.

- Safety Analysis Set (SAS)

Patients included in the SAS 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 subgroups 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 ≤24 letters / 24 letters < BCVA <70 letters / 70 letters ≤ BCVA,
- BCVA at inclusion: BCVA ≤39 letters / 39 letters < BCVA <60 letters / 60 letters ≤ BCVA,
- BCVA at inclusion: BCVA ≤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 treatments 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:

- Number and % of patients who experienced at least one concomitant ophthalmological surgery,
- Number and % of patients who experienced at least one cataract surgery,
- Number and % of patients who experienced at least one filtration surgery,
- Number and % of patients who experienced at least one vitrectomy,
- Number and % of patients who experienced at least one internal limiting membrane peeling,
- Number 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 change in BCVA from baseline is also presented according to the following classes:

- Change in BCVA $\leq$-15 letters (i.e. loss of at least 3 lines),
- Change in BCVA]-15, - 10] letters (i.e. loss of at least 2 lines),
- Change in BCVA]-10, -5] letters,
- Change in BCVA]-5, 0[letters,
- Change in BCVA [0; 5[letters,
- Change in BCVA [5, 10[letters,
- Change in BCVA [10, 15[letters (i.e. gain of at least 2 lines),

- Change in BCVA ≥ 15 letters (i.e. gain of at least 3 lines).

The number and % of patients who achieved BCVA score ≥70 letters is also presented.

For the BCVA missing values in the FAS, two different robustness analyses were performed (see section **Erreur ! Source du renvoi introuvable.**).

The BCVA change from baseline is also presented:

- According to the BCVA classes at inclusion,
- 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.),
- According to loading dose status (received / not received) among treatment-naïve patients.

9.9.2.6 Secondary outcomes 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 (treatment-naïve / previously treated) on the FAS and on the Target FAS. The same two robustness analyses were conducted as for the primary outcome.

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.

- Change in central retinal thickness (CRT)

The mean change in 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.

The number and % of patients who achieved CRT <250 µm is also presented.

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

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

- Presence of fluid in OCT

Analyses were performed overall and according to treatment status (treatment-naïve / previously treated) on the FAS. 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.

- Change in fluorescein angiography (FA) and fundus photography (FP) outcomes

The change in FA and FP outcomes between baseline and 24 months were presented overall and according to treatment status (treatment-naïve / previously treated) on the FAS 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.

- Vital signs and laboratory parameters

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 are provided.

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

- DME monitoring

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

- Number of visits per patient (monitoring only / combined) over 6 months, over 12 months and over 24 months,
- Number and % of patients with exactly *n* follow-up visits at 6, 12 and 24 months,
- Number and % of patients with exactly *n* follow-up visits with monitoring only at 6, 12 and 24 months,
- Number of visits for diabetes per patient (diabetologist),
- Number of visits with OCT assessment per patient over 24–month follow-up,
- Number of visits with FP per patient after 24 months,
- Number of visits with FA per patient after 24 months,
- Number of visits with VA assessment per patient after 24 months.

9.9.2.7 Safety analysis

Safety analysis was performed on the SAS.

AEs considered for this analysis are treatment-emergent adverse events (TEAE), i.e. AEs which occurred after the first injection of IVT aflibercept and up to 30 days after the last 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 TEAE requiring special attention as per defined by the risk management plan (RMP) and a listing of all AE which are not TEAE are also presented.

All "off-label use" TEAE related to EYLEA® were described separately from other treatment-related TEAE in a listing. "Off-label use" TEAE were defined as TEAEs with a PT in the following list: Product use issue, Inappropriate schedule of drug administration, Off label use, Inappropriate schedule of product administration and Incorrect dose administered.

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 TEAE,
- Any/All serious TEAE,
- Any/All treatment-related TEAE,
- Any/All treatment-related "off-label use" TEAE
- Any/All TEAE related to procedure,
- Any/All TEAE leading to treatment withdrawal,
- Any/All serious treatment-related TEAE,
- Any/All serious TEAE leading to treatment withdrawal,
- Any/All TEAE leading to death.

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

9.9.3 Missing values

Missing data for BCVA were replaced according to 2 different imputation methods (see Section 9.9.4).

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 AE, if the date was missing, AE was considered by default as TEAE, except in particular situations where the available information was sufficient to ensure that the AE was not emergent.

Regarding the relationship of an AE to the treatment, if the investigator refused to make a decision on the relationship of the AE to EYLEA® despite the required follow-up attempts, the AE was considered by default as related to EYLEA®.

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

Sensitivity analyses have been performed for the change in BCVA and CRT from baseline to 6, 12 and 24 months. These sensitivity analyses consisted in replacing missing BCVA / CRT using 2 different imputation methods:

- Median imputation: in each subgroup (treatment-naive patients / previously treated patients), the median for the BCVA / CRT at a dedicated timepoint (i.e 6 months, 12 months or 24 months) were computed and the corresponding BCVA / CRT missing values were replaced by the subgroup median of the dedicated timepoint (i.e. 6 months, 12 months or 24 months) depending on the patient subgroup.
- Markov Chain Monte Carlo (MCMC) imputation: in case of missing BCVA / CRT at a dedicated timepoint, the missing values were replaced according to the patient's previous BCVA / CRT results based on a MCMC algorithm with 10000 iterations.

9.9.5 Amendments to the statistical analysis plan

Changes to the planned analyses from the study protocol have been performed and are described in the statistical analysis plan which is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

- On the one hand, subgroup analyses according to initial HbA1c level, baseline BCVA 25, baseline BCVA 70-75 and baseline BCVA/CRT combined were deleted. On the other hand, additional subgroups were defined for the analyses related to treatment exposure, according to the loading dose status, according to the number of injections received within the first 3 months, according to the overtreatment status, and according to baseline BCVA. Moreover, all statistical analyses were planned to be performed according to patient status (i.e. treatment-naïve vs. previously treated patients).
- The time window for the timepoint at 6 months was extended to include 5 months evaluations. The time window was defined as [4.5 ; 6.5[months instead of [5.5; 6.5[months. The timepoint at 5 months was therefore not considered anymore (especially for graphs of mean BCVA at each month).
- LOCF analyses were deleted and replaced by sensitivity analyses using imputation by MCMC method for the change from baseline in BCVA and CRT at 12 months (see Section 9.9.4).
- As regards the anatomical and functional changes from baseline, 6-month data were analyzed in addition to 12- and 24-month data. Moreover, the proportion of patients who reached the BCVA score of 70 letters, the number of lines (according to BCVA score) gained and loosed and the proportion of patients who achieved a CRT <250 µm are described at each timepoint (6, 12 and 24 months).
- As regards the DME monitoring and the IVT aflibercept regimen, 6-month data were analyzed in addition to 12- and 24-month data, but analyses related to the number of monitoring visits for diabetes, the number of OCT, FP, FA and VA assessments were performed at 24 months only.

Additionally, post-hoc analyses (not included in the SAP) have also been performed on treatment-naïve patients to assess the number of injections received at 6, 12 and 24 months according to the loading dose status. Additional analysis on patients who switched to another DME treatment have also been performed. These additional analyses are provided in the chapter 12 of the Tables Figures and Listing which is kept as is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

9.10 Quality control

9.10.1 Data management process

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 PPD.

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). A Data Management Report (DMR) documents all activities actually performed throughout the data management process of the study.

The DMP/DMR is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

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.

The MRP is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

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 kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

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 kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

9.10.3 Storage of records and archiving

The sponsor made sure that all relevant documents of this study including CRFs and other de-identified collected patient records are stored after end or discontinuation of the study at least for 10 years. Other instructions for storage of medical records remain unaffected.

The treating ophthalmologists participating in the study had 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 15 years.

PPD sent to Bayer, the database and statistical programming performed to generate results; they are stored on Bayer environment.

10. Results

The full analyses are presented in the final version of the Tables, Figures and Listings which is kept as is kept as stand-alone documents (see Annex 1: List of stand-alone documentsand is available upon request.

10.1 Participants

From 15 SEP 2016 to 05 JUL 2017, 56 ophthalmologists participated in the study and contributed 402 patients, 377 (93.8%) of whom are included in the FAS.

Disposition of physicians and disposition of patients are summarized in Table 4 and Table 5.

Table 4: Physician disposition

		N = 118
Physicians offered to participate	N	118
Physicians who agreed to participate	n (%)	63 (53.4%)
Site initiation	n (%)	61 (51.7%)
Active physicians [a]	n (%)	56 (47.5%)
[a] Physicians who included at least one patient		

Reference: Global Monitoring Report kept as stand-alone documents (see Annex 1: List of stand-alone documentsand available upon request

Table 5: Patient disposition

		Enrolled N = 402
Patients enrolled in the study	N	402
Patients included in the Safety Analysis Set (SAS)	n (%)	389 (96.8%)
Reason for exclusion from the SAS	N	13
No IVT-AFL injection in any of the eye	*n (%)*	*13 (100.0%)*
Patients included in the Full Analysis Set (FAS)	n (%)	377 (93.8%)
Reason for exclusions from the FAS [a]	N	25
Screening failure	*n (%)*	*19 (76.0%)*
No BCVA evaluation at baseline	*n (%)*	*15 (60.0%)*
No IVT-AFL injection in the study eye	*n (%)*	*13 (52.0%)*
Patients excluded from the SAS	*n (%)*	*13 (52.0%)*
Patient included in the Target FAS [b]	n (%)	194 (48.3%)
[a] a patient may have several reasons for exclusion of the analysis set [b] patients included in the FAS with a BCVA available at 12 months (i.e. between 11 and 13 months from the first IVT-AFL injection BCVA, best-corrected visual acuity; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; SAS, safety analysis set		

Reference: Table 1.1 in Tables Figures and Listings.

Early study discontinuations are summarized in Table 6 on the FAS.

One hundred and forty-eight (39.3%) patients from the FAS terminated the study prematurely, mainly to switch to another treatment (n=57; 15.1%) or because they were lost to follow-up (n=65; 17.2%). Overall, 49 (13.0%) patients switch to another treatment because of a lack of efficacy or consecutively

to ophthalmologist decision, 5 (1.3%) patients switched because of an adverse event and 3 (0.8%) patients to switch at their own request. Most patients (n=42; 11.1%) switched to Ozurdex® (i.e. dexamethasone). Additional post-hoc analyses on switched patients are provided in Section 10.5.5.

Table 6: Early study discontinuation (FAS, N=377)

		FAS N = 377
Patients who terminated the study prematurely [a]	n (%)	148 (39.3%)
Early termination, primary reason	N (missing value)	147 (1)
Change of treating ophthalmologist	n (%)	11 (7.5%)
Death	n (%)	7 (4.8%)
Withdrawal of consent/Patient decision	n (%)	4 (2.7%)
Lost to follow-up	n (%)	65 (44.2%)
Treating ophthalmologist decision	n (%)	3 (2.0%)
Switch to another treatment	n (%)	57 (38.8%)
Switch to dexamethasone, IVT implant	n (%)	42 (28.6%)
Switch to ranibizumab, IVT	n (%)	13 (8.8%)
Switch to other treatment [b]	n (%)	2 (1.4%)
Main reason for switching to another treatment	N	57
Lack of efficacy / no responder	n (%)	32 (56.1%)
Treating ophthalmologist decision	n (%)	17 (29.8%)
Adverse event	n (%)	5 (8.8%)
Patient decision	n (%)	3 (5.3%)

[a] Excluding patients who discontinued the study because of end of follow-up.
[b] Vitrectomy for one patient and bevacizumab for one patient.
FAS, full analysis set; IVT, intravitreal.

Reference: Table 1.3 in Tables Figures and Listings

Overall on the FAS, 206 (54.6%) patients were treatment-naïve and 171 (45.4%) were previously treated. The main subgroups defined for the statistical analyses are presented in Table 7 on the FAS overall and according to treatment status.

Table 7: Subgroup disposition (FAS, N=377)

Baseline BCVA			**Treatment-naïve N = 206**	**Previously treated N = 171**	**Total N = 377**
24-70	≤24 letters	n (%)	8 (3.9%)	7 (4.1%)	15 (4.0%)
	24–70 letters	n (%)	139 (67.5%)	125 (73.1%)	264 (70.0%)
	≥70 letters	n (%)	59 (28.6%)	39 (22.8%)	98 (26.0%)
39-60	≤39 letters	n (%)	21 (10.2%)	26 (15.2%)	47 (12.5%)
	39–60 letters	n (%)	50 (24.3%)	46 (26.9%)	96 (25.5%)
	≥60 letters	n (%)	135 (65.5%)	99 (57.9%)	234 (62.1%)
65	≤65 letters	n (%)	122 (59.2%)	106 (62.0%)	228 (60.5%)
	>65 letters	n (%)	84 (40.8%)	65 (38.0%)	149 (39.5%)

BCVA, best-corrected visual acuity; FAS, full analysis set.

Reference: Table 2.1.1.2 in Tables Figures and Listings.

10.2 Descriptive data

10.2.1 Characteristics of participating ophthalmologists

All data related to participating ophthalmologists are detailed in the chapter 11 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Active physicians were mainly men (53.6%), hospital practitioners (57.1% public hospital, 17.9% private hospital), aged between PPD (53.6%). They were mainly located in Ile-de-France (23.2%), in Occitanie (12.5%), in Auvergne Rhône-Alpes (10.7%), in Provence-Alpes Côte d'Azur Corse (10.7%) and in Centre Val de Loire (8.9%).

10.2.2 Patients' baseline characteristics

All data related to patient baseline characteristics are detailed in the chapters 2.1.2, 2.1.3, 2.1.4, 2.1.5, 2.2.2, 2.2.3, 2.2.4 and 2.2.5 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

General baseline characteristics are summarized in Table 8 on the FAS overall and according to the treatment status.

Patients had mean (±SD) age of 65.9 (±11.1) years (range, 19-91 years) and were slightly more male (55.7%). Less than 10% of patients were current smokers and 28.7% were former smokers.

Mean (±SD) time since DME diagnosis for study eye was 7.1 (±17.8) months in treatment-naïve patients and 39.0 (±38.8) in previously treated patients. Median times were 1.2 month and 28.6 months, respectively.

Approximately three quarter of the patients (74.0%) suffered from hypertension and one third (34.8%) had cardiovascular disease history. Few patients had stroke history (5.2%) or transient ischemic attack history (2.0%).

Mean (±SD) body mass index was 29.1 (±5.8) kg/m² and mean (±SD) blood pressure was 142 (±19) / 78 (±12) 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.

Table 8: General baseline characteristics (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Age, years	N	206	171	377
	Mean ± SD	64.8 ± 12.0	67.2 ± 9.8	65.9 ± 11.1
	Median	65.0	67.0	66.0
	Q1 ; Q3	57.0 ; 73.0	61.0 ; 74.0	59.0 ; 73.0
	Min ; Max	19 ; 90	31 ; 91	19 ; 91
Gender, male	n (%)	120 (58.3%)	90 (52.6%)	210 (55.7%)
Smoking status	N (missing values)	171 (35)	143 (28)	314 (63)
Current smoker	n (%)	17 (9.9%)	11 (7.7%)	28 (8.9%)
Former smoker	n (%)	51 (29.8%)	39 (27.3%)	90 (28.7%)
BMI, kg/m²	N (missing values)	126 (80)	111 (60)	237 (140)
	Mean ± SD	28.8 ± 6.2	29.5 ± 5.4	29.1 ± 5.8
	Median	27.7	28.8	28.4
	Q1 ; Q3	24.8 ; 31.2	25.8 ; 33.1	25.2 ; 32.0
	Min ; Max	17 ; 50	18 ; 46	17 ; 50
SBP, mmHg	N (missing values)	83 (123)	76 (95)	159 (218)
	Mean ± SD	141.6 ± 20.3	141.5 ± 17.9	141.5 ± 19.1
	Median	140.0	140.0	140.0
	Q1 ; Q3	125.0 ; 160.0	130.0 ; 150.0	130.0 ; 153.0
	Min ; Max	109 ; 194	100 ; 200	100 ; 200
DBP, mmHg	N (missing values)	83 (123)	74 (97)	157 (220)
	Mean ± SD	77.6 ± 12.5	78.0 ± 11.5	77.8 ± 12.0
	Median	80.0	80.0	80.0
	Q1 ; Q3	70.0 ; 88.0	70.0 ; 85.0	70.0 ; 88.0
	Min ; Max	44 ; 110	40 ; 100	40 ; 110
Time since DME diagnosis [a], months	N (missing values)	204 (2)	167 (4)	371 (6)
	Mean ± SD	7.17 ± 17.82	38.96 ± 38.78	21.48 ± 33.16
	Median	1.17	28.58	6.44
	Q1 ; Q3	0.36 ; 4.02	11.70 ; 50.89	0.85 ; 30.46
	Min ; Max	0.0 ; 120.5	0.0 ; 258.2	0.0 ; 258.2
Hypertension	N (missing values)	195 (11)	163 (8)	358 (19)
	n (%)	132 (67.7%)	133 (81.6%)	265 (74.0%)
Cardiovascular disease	N (missing values)	178 (28)	158 (13)	336 (41)
	n (%)	58 (32.6%)	59 (37.3%)	117 (34.8%)
Stroke	N (missing values)	186 (20)	159 (12)	345 (32)
	n (%)	12 (6.5%)	6 (3.8%)	18 (5.2%)
TIA	N (missing values)	186 (20)	159 (12)	345 (32)
	n (%)	3 (1.6%)	4 (2.5%)	7 (2.0%)

[a] Related to study eye only
BMI, body mass index; DBP, diastolic blood pressure; DME, diabetic macular edema; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

Reference: Tables 2.1.2.1, 2.1.2.2, 2.1.2.3, 2.1.2.4, 2.1.3.1.1 and 2.1.3.3.1 in Tables Figures and Listings.

Diabetes baseline characteristics are summarized in Table 9 on the FAS overall and according to the treatment status.

Mean (±SD) time since diabetes diagnosis was 17.5 (±12.2) years for treatment-naïve patients and 19.3 (±11.4) years for previously treated patients.

Mean (±SD) glycemia was 13.0 (±15.6) mmol/L in treatment-naïve patients compared to 8.4 (±8.1) 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) glycated hemoglobin was 7.7 (±1.4) % which reflect the underlying condition of the patients suffering from diabetes (>6%). However, mean HbA1c level did not significantly differ in treatment-naïve and previously treated patients.

Table 9: Diabetes baseline characteristics (FAS, N=377)

		Treatment-naïve N = 206	**Previously treated N = 171**	**Total N = 377**
Time since diabetes diagnosis, years	N	188 (18)	158 (13)	346 (31)
	Mean ± SD	17.5 ± 12.2	19.3 ± 11.4	18.3 ± 11.9
	Median	16.0	18.0	17.0
	Q1 ; Q3	8.0 ; 25.0	11.0 ; 26.0	10.0 ; 25.0
	Min ; Max	0 ; 50	2 ; 63	0 ; 63
Glycemia, mmol/L	N	46 (160)	36 (135)	82 (295)
	Mean ± SD	13.0 ± 15.6	8.4 ± 8.1	11.0 ± 13.0
	Median	8.3	7.0	7.3
	Q1 ; Q3	6.2 ; 10.5	5.3 ; 8.6	5.7 ; 9.4
	Min ; Max	4 ; 83	1 ; 52	1 ; 83
HbA1c, %	N	124 (82)	100 (71)	224 (153)
	Mean ± SD	7.8 ± 1.5	7.5 ± 1.3	7.7 ± 1.4
	Median	7.7	7.4	7.5
	Q1 ; Q3	6.8 ; 8.5	6.6 ; 8.2	6.7 ; 8.4
	Min ; Max	5 ; 15	5 ; 12	5 ; 15

FAS, full analysis set; HbA1c, glycated hemoglobin; Q1, first quartile; Q3, third quartile; SD, standard deviation

Reference: Tables 2.1.2.5 and 2.1.3.1.1 in Tables Figures and Listings.

History of ophthalmological surgery is summarized in Table 10 on the FAS overall and according to the treatment status.

Overall, 145 (40.4%) patients had experienced at least one previous ophthalmological surgery, mainly cataract surgery (132 patients; 36.8%). Prior cataract surgery was more frequent in patients previously treated for DME (46.4% vs. 28.5% in treatment-naïve patients).

Table 10: Prior ophthalmological surgeries (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Prior ophthalmological surgery [a]	N (missing values)	193 (13)	166 (5)	359 (18)
	n (%)	64 (33.2%)	81 (48.8%)	145 (40.4%)
Cataract surgery	n (%)	55 (28.5%)	77 (46.4%)	132 (36.8%)
Filtration surgery	n (%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Vitrectomy	n (%)	6 (3.1%)	7 (4.2%)	13 (3.6%)
ILM peeling	n (%)	2 (1.0%)	6 (3.6%)	8 (2.2%)
Other surgery	n (%)	10 (5.2%)	1 (0.6%)	11 (3.1%)

[a] Prior ophthalmological surgeries related to study eye only. FAS, full analysis set; ILM, internal limiting membrane.

Reference: Table 2.1.3.2.1 in Tables Figures and Listings.

An overview of prior DME treatments is presented in Table 11 on the FAS.

Among previously treated patients (n=171), approximately two third (66.5%) of patients had been previously treated with IVT anti-VEGF agents in the study eye (mainly with ranibizumab [102 patients, 63.4%]), 64.8% of patients had been previously treated with photocoagulation laser (mainly pan-photocoagulation laser [70 patients, 42.4%]) in the study eye and 27.3% of patients had been previously injected with intraocular steroids in the study eye.

Table 11: Prior DME treatments in previously treated patients (FAS, n=171)

		Previously treated N = 171
Time since last DME treatment (months) [a]	N (missing values)	153 (18)
	Mean ± SD	9.84 ± 13.65
	Median	4.53
	Q1 ; Q3	1.71 ; 10.58
	Min ; Max	0.0 ; 72.0
Photocoagulation laser [a]	N (missing values)	165 (6)
Prior Laser (all type)	n (%)	107 (64.8%)
Macular	n (%)	33 (20.0%)
Pan-photocoagulation	n (%)	70 (42.4%)
Macular grid	n (%)	3 (1.8%)
Intraocular steroids [a] [b]	N (missing values)	165 (6)
Prior IVT steroid	n (%)	45 (27.3%)
Anti-VEGF treatment other than IVT-AFL [a]	N (missing values)	161 (10)
Prior IVT anti-VEGF (all drug) [b]	n (%)	107 (66.5%)
Ranibizumab only	n (%)	94 (58.4%)
Ranibizumab and bevacizumab	n (%)	8 (5.0%)
Bevacizumab only	n (%)	4 (2.5%)
Bevacizumab and pegaptanib	n (%)	1 (0.6%)

[a] For the study eye only. [b] A patient may have previously received several anti-VEGF agents.
DME, diabetic macular edema; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation; VEGF, vascular endothelial growth factor.

Reference: Table 2.1.3.3.2 in Tables Figures and Listings.

10.2.3 Concomitant and adjunctive therapies

All data related to concomitant and adjunctive therapies are detailed in the chapters 2.1.5 and 2.2.5 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

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) and surgeries is presented in Table 12, Table 13 and Table 14 on the FAS overall and according to the treatment status. Table 12 summarizes categories of medication administered in at least 10% of the patients, Table 13 summarizes categories of ophthalmological medication administered in at least 5% of the patients and Table 14 summarizes concomitant ophthalmological surgeries.

A large majority of patients (91.5%) received at least one concomitant medication during the observational study period, mainly non-ophthalmological medication (88.1%) (see Tables, Figures and Listings in Annex 1: List of stand-alone documents, Table 2.1.5.2). The most common medications used were drugs used in diabetes (85.7%), agents acting on the renin-angiotensin system (53.1%), lipid modifying agents (45.4%) and analgesics (38.5%). Approximately one third of patients (31.3%) received a concomitant ophthalmological medication, mainly anti-infectives (8.0%), beta blocking agents (6.6%), non-steroidal anti-inflammatory agents (5.8%) and sympathomimetics in glaucoma therapy (5.3%). All concomitant medications (ophthalmological and non-ophthalmological) are detailed according to their ATC level 2 and 4 on the FAS overall and according to the treatment status in Tables, Figures and Listings in Annex 1: List of stand-alone documents (Tables 2.1.5.3 and 2.1.5.5).

Overall, 66 (17.5%) patients experienced at least one concomitant ophthalmological surgery in the study eye within the study observational period, mainly cataract surgery (12.5%).

Table 12: Overview of concomitant non-ophthalmological medications (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Concomitant non-ophthalmological medication	n (%)	178 (86.4%)	154 (90.1%)	332 (88.1%)
Drugs used in diabetes	n (%)	175 (85.0%)	148 (86.5%)	323 (85.7%)
Agents acting on the renin-angiotensin system	n (%)	102 (49.5%)	98 (57.3%)	200 (53.1%)
Lipid modifying agents	n (%)	97 (47.1%)	74 (43.3%)	171 (45.4%)
Analgesics	n (%)	78 (37.9%)	67 (39.2%)	145 (38.5%)
Beta blocking agents	n (%)	40 (19.4%)	53 (31.0%)	93 (24.7%)
Calcium channel blockers	n (%)	42 (20.4%)	37 (21.6%)	79 (21.0%)
Diuretics	n (%)	37 (18.0%)	40 (23.4%)	77 (20.4%)
Antithrombotic agents	n (%)	42 (20.4%)	33 (19.3%)	75 (19.9%)
Drugs for acid related disorders	n (%)	44 (21.4%)	30 (17.5%)	74 (19.6%)
Psychoanaleptics	n (%)	27 (13.1%)	16 (9.4%)	43 (11.4%)
Antiepileptics	n (%)	19 (9.2%)	21 (12.3%)	40 (10.6%)

Non-ophthalmological concomitant medications are medications received by the patient for other purpose than DME. Categories of medications are ATC classification level 2 (therapeutic main group) with frequency >10%. A patient may have had received several medications.
ATC, anatomical therapeutic chemical; DME, diabetic macular edema; FAS, full analysis set.

Reference: Table 2.1.5.5 in Tables Figures and Listings.

Table 13: Overview of concomitant ophthalmological medications and surgeries (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Concomitant ophthalmological medication	n (%)	66 (32.0%)	52 (30.4%)	118 (31.3%)
Beta blocking agents	n (%)	7 (3.4%)	18 (10.5%)	25 (6.6%)
Antiinflammatory agents, non-steroids	n (%)	10 (4.9%)	12 (7.0%)	22 (5.8%)
Sympathomimetics in glaucoma therapy	n (%)	10 (4.9%)	10 (5.8%)	20 (5.3%)
Prostaglandin analogues	n (%)	9 (4.4%)	9 (5.3%)	18 (4.8%)
Other antiinfectives	n (%)	13 (6.3%)	17 (9.9%)	30 (8.0%)

Ophthalmological concomitant medications are ophthalmological medications received in the study eye for other purpose than DME. A patient may have had received several medications.
Categories of medications are ATC classification level 2 (therapeutic main group) with frequency >5%.
ATC, anatomical therapeutic chemical; DME, diabetic macular edema; FAS, full analysis set.

Reference: Table 2.1.5.3 in Tables Figures and Listings.

Table 14: Overview of concomitant ophthalmological surgeries (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Concomitant ophthalmological surgery	n (%)	36 (17.5%)	30 (17.5%)	66 (17.5%)
Cataract surgery	n (%)	24 (11.7%)	23 (13.5%)	47 (12.5%)
Vitrectomy	n (%)	3 (1.5%)	3 (1.8%)	6 (1.6%)
ILM peeling	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Other surgical procedure	n (%)	13 (6.3%)	6 (3.5%)	19 (5.0%)

Ophthalmological concomitant surgeries are ophthalmological surgeries received in the study eye for other purpose than DME. A patient may have had experienced several surgeries.
DME, diabetic macular edema; FAS, full analysis set; ILM, internal limiting membrane.

Reference: Table 2.1.5.6 in Tables Figures and Listings.

An overview of adjunctive therapies (i.e. DME treatment, other than IVT aflibercept, received by the patient during the course of the study) is presented in Table 15.

Overall, 69 (18.3%) patients have received at least one adjunctive therapy during the study observational period, mainly laser therapy (64 patients; 17%).

Six patients (1.6%) have received at least one adjunctive medication in the study eye before switching back to IVT aflibercept treatment. Details on these patients are provided in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listing 12.1.5.1. Although corticosteroids are not part of the standard of care for DME anymore, corticosteroids were the most frequent adjunctive medication administered (4 patients). Within the present analysis, these patients were not withdrawn from the study following the administration of adjunctive medication and were therefore not considered as switched patients.

Table 15: Overview of adjunctive therapies (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Adjunctive therapy, all type	n (%)	34 (16.5%)	35 (20.5%)	69 (18.3%)
Adjunctive laser therapy	n (%)	32 (15.5%)	32 (18.7%)	64 (17.0%)
Macular laser	n (%)	11 (5.3%)	14 (8.2%)	25 (6.6%)
Pan-photocoagulation laser	n (%)	24 (11.7%)	21 (12.3%)	45 (11.9%)
Adjunctive medication	n (%)	2 (1.0)	4 (2.3)	6 (1.6)
Corticosteroids	n (%)	2 (1.0)	2 (1.2)	4 (1.1)
Antineovascularisation agents	n (%)	0 (0.0)	2 (1.2)	2 (0.5)

Adjunctive therapies are DME treatments, other than IVT-AFL, received by the patient in the study eye during the course of the study. A patients may have had several adjunctive therapies.
Categories of medications are ATC classification level 4 (chemical subgroup) and belong to therapeutic main group (i.e. ATC level 2) 'Ophthalmologicals'.
ATC, anatomical therapeutic chemical; DME, diabetic macular edema; FAS, full analysis set, IVT-AFL, intravitreal aflibercept.

Reference: Tables 2.1.5.7 and 2.1.5.8 in Tables Figures and Listings.

10.2.4 Treatment exposure

All data related to treatment exposure are detailed in the chapter 3 of the of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Reasons for starting IVT aflibercept are summarized in Table 16 on the FAS according to the treatment status. Almost all treatment-naïve patients (94.7%) started IVT aflibercept treatment because of a decrease of visual acuity due to DME. For previously treated patients, the main reason for starting IVT aflibercept treatment was the insufficient efficacy of previous DME treatments (78.2%). The reason was unknown for 11.9% of the patients.

Table 16: Reasons for starting IVT-AFL treatment (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171
Reasons for starting IVT-AFL	N (missing values)	206	170 (1)
Decrease of VA due to DME	n (%)	195 (94.7%)	NA
Early care of DME	n (%)	22 (10.7%)	NA
Macular laser not indicated	n (%)	21 (10.2%)	NA
Vitrectomy not indicated	n (%)	19 (9.2%)	NA
Diabetes care not optimized	n (%)	8 (3.9%)	NA
Diabetes care optimized but insufficient	n (%)	15 (7.3%)	NA
Insufficient efficacy of prior DME treatment [a]	n (%)	NA	133 (78.2%)
AE occurred with prior DME treatment	n (%)	NA	1 (0.6%)
Do not pronounce	n (%)	9 (4.4%)	36 (21.2%)

[a] According to investigator's judgment
AE, adverse event; DME, diabetic macular edema; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; NA, not applicable; VA, visual acuity.

Reference: Table 3.1.1 in Tables Figures and Listings.

The number of IVT aflibercept injections received per patients and per period are summarized in Table 17 on the FAS overall and according to the treatment status.

The mean (±SD) number of injections received per patient during the first 6-month follow-up period was 4.9 (±1.4) injections. The median number of injections was 5 (Q1, 4; Q3, 6) and no difference was observed between treatment-naïve and previously treated patients.

Over the first 12-month follow-up period, the patients received a mean (±SD) number of injections of 7.3 (±2.6). The median number of injections was of 7.5 and no difference was observed between treatment-naïve and previously treated patients.

For the patients who were followed 24 months, the mean (±SD) number of injections received per patient was 11.6 (±4.8). The median number of injections was 12 (Q1, 8; Q3, 15). No difference was observed between treatment-naïve and previously treated patients.

Overall 542 eyes were injected with IVT aflibercept within the study observational period and 165 (43.8%) patients received bilateral injections (see Table 12.3.1 in Tables Figures and Listings). For the purpose of the analysis, the eye with the worst visual acuity at baseline was considered as the study eye (see Section 9.3).

Table 17: Number of IVT-AFL injections received overtime (FAS, N=377)

		Treatment-naïve N = 206	**Previously treated N = 171**	**Total N = 377**
Number of injections at 6 months [a]	N	182	156	338
	Mean ± SD	5.0 ± 1.4	4.8 ± 1.4	4.9 ± 1.4
	Median	5.0	5.0	5.0
	Q1 ; Q3	4.0 ; 6.0	4.0 ; 6.0	4.0 ; 6.0
	Min ; Max	1 ; 8	1 ; 8	1 ; 8
Number of injections at 12 months [b]	N	149	141	290
	Mean ± SD	7.4 ± 2.6	7.2 ± 2.6	7.3 ± 2.6
	Median	8.0	7.0	7.5
	Q1 ; Q3	5.0 ; 9.0	5.0 ; 9.0	5.0 ; 9.0
	Min ; Max	1 ; 13	2 ; 13	1 ; 13
Number of injections at 24 months [c]	N	79	89	168
	Mean ± SD	11.3 ± 4.9	11.9 ± 4.7	11.6 ± 4.8
	Median	12.0	12.0	12.0
	Q1 ; Q3	8.0 ; 14.0	8.0 ; 15.0	8.0 ; 15.0
	Min ; Max	1 ; 23	2 ; 23	1 ; 23

[a] Data computed for patients followed at least 6 months (i.e. follow-up data up to 4.5).
[b] Data computed for patients followed at least 12 months (i.e. follow-up data available up to 11 months)
[c] Data computed for patients followed at least 24 months (i.e. follow-up data available up to 23 months)
FAS, full analysis set, IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Table 3.1.1 in Tables Figures and Listings.

The number of IVT aflibercept injections received per patients and per period in treatment-naïve patients with a BCVA available are summarized in Table 18 according to the loading dose status.

Table 18: Number of IVT-AFL injections received overtime in treatment-naïve patients (FAS, treatment-naïve patients, N=206)

		Loading dose received N = 84	Loading dose not received N = 122	Total N = 206
Number of injections at 6 months [a]	N	68	57	125
	Mean ± SD	5.6 ± 0.5	4.9 ± 1.6	5.3 ± 1.2
	Median	6.0	5.0	5.0
	Q1 ; Q3	5.0 ; 6.0	4.0 ; 6.0	5.0 ; 6.0
	Min ; Max	5 ; 7	1 ; 8	1 ; 8
Number of injections at 12 months [b]	N	51	50	101
	Mean ± SD	8.1 ± 1.7	7.3 ± 2.9	7.7 ± 2.4
	Median	8.0	7.0	8.0
	Q1 ; Q3	7.0 ; 9.0	5.0 ; 9.0	6.0 ; 9.0
	Min ; Max	5 ; 12	2 ; 13	2 ; 13
Number of injections at 24 months [c]	N	25	29	54
	Mean ± SD	12.6 ± 3.4	11.1 ± 6.1	11.8 ± 5.1
	Median	13.0	11.0	12.0
	Q1 ; Q3	11.0 ; 14.0	6.0 ; 16.0	8.0 ; 16.0
	Min ; Max	5 ; 20	1 ; 23	1 ; 23

[a] Data computed for patients followed at least 6 months (i.e. follow-up data up to 4.5) and with a BCVA available at 6 months (i.e. between 4.5 and 6.5 months).
[b] Data computed for patients followed at least 12 months (i.e. follow-up data available up to 11 months) and with a BCVA available at 12 months (i.e. between 11 and 13 months)
[c] Data computed for patients followed at least 24 months (i.e. follow-up data available up to 23 months) and with a BCVA available at 24 months (i.e. between 23 and 25 months)
FAS, full analysis set, IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Tables 12.1.2.1, 12.1.2.2 and 12.12.3 in Tables Figures and Listings.

The mean (±SD) number of injections received per patient during the first 6-month follow-up period in patients with a BCVA available at 6 months was 5.6 (±0.5) injections in those who received the loading dose and 4.9 (±1.6) in those who did not received the loading dose. The median number of injections was 6 (Q1, 5; Q3, 6) in patients who received the loading dose and 5 (Q1, 4; Q3, 6) in those who did not received the loading dose.

Over the first 12-month follow-up period, the mean (±SD) number of injections received per patient in patients with a BCVA available at 12 month was 8.1 (±1.7) in those who received the loading dose and 7.3 (±2.9) in those who did not received the loading dose. The median number of injections was 8 (Q1, 7; Q3, 9) in patients who received the loading dose and 7 (Q1, 5; Q3, 9) in those who did not received the loading dose.

For the patients who were followed 24 months, the mean (±SD) number of injections received per patient in patients with a BCVA available at 24 month was 12.6 (±3.4) in those who received the loading dose and 11.1 (±6.1) in those who did not received the loading dose. The median number of injections was 13 (Q1, 11; Q3, 14) in patients who received the loading dose and 11 (Q1, 6; Q3, 16) in those who did not received the loading dose.

Main reason for permanent discontinuation of IVT aflibercept is summarized in Table 19 on the FAS overall and according to the treatment status.

During the study, 105 (27.9%) patients discontinued IVT aflibercept permanently, mainly to switch to another treatment (52 patients; 13.8%). Dexamethasone (IVT implant) was the most common treatment prescribed (36 patients; 9.5%). Five patients permanently stopped IVT aflibercept consecutively to an adverse event: for 3 patients, AEs were assessed as possibly related to IVT aflibercept injection but were all resolved (skin reaction, stroke and acute coronary syndrome); for the 2 others, the AEs (anxiety attack and myocardial infarction) were not related to IVT aflibercept (see Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listing 3.1.1).

Table 19: Permanent discontinuation of IVT-AFL (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
IVT-AFL discontinuation	n (%)	58 (28.2%)	47 (27.5%)	105 (27.9%)
Main reason for IVT-AFL discontinuation [a]				
Adverse event	n (%)	3 (1.5%)	2 (1.2%)	5 (1.3%)
Withdrawal of consent/Patient decision	n (%)	13 (6.3%)	7 (4.1%)	20 (5.3%)
Treating ophthalmologist decision	n (%)	8 (3.9%)	11 (6.4%)	19 (5.0%)
Switch to another treatment [a] [b]	n (%)	28 (13.6%)	24 (14.0%)	52 (13.8%)
Dexamethasone, IVT implant	n (%)	17 (8.3%)	19 (11.1%)	36 (9.5%)
Ranibizumab, IVT	n (%)	8 (3.9%)	5 (2.9%)	13 (3.4%)
Triamcinolone, IVT	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Vitrectomy	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Unknown	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Lost to follow-up	n (%)	3 (1.5%)	3 (1.8%)	6 (1.6%)
Ophthalmologist change	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Visual acuity recovery	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Death	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)

[a] Only primary reason was recorded; a patient may have discontinued IVT-AFL for another reason than switch to another treatment, and then switched later to another DME treatment that led to premature study discontinuation.
[b] 12 additional patients switched to another treatment but were not recorded as switched patients by the investigators in the eCRF; out of them 6 patients switched back to IVT aflibercept and the remaining 6 did not received any additional injections of IVT aflibercept.
FAS, full analysis set, IVT, intravitreal; IVT-AFL, intravitreal aflibercept.

Reference: Table 3.1.1 and Listing 3.1.2 in Tables Figures and Listings.

10.3 Outcome data

Out of the 377 from the FAS, 338 patients were followed at least 6 months, 290 patients were followed at least 12 months and 168 patients were followed at least 24 months (see Tables, Figures and Listings in Annex 1: List of stand-alone documents, Table 3.1.1).

Table 20 summarizes the number of BCVA and CRT data available at baseline, 6 months, 12 months and 24 months on the FAS overall and according to the treatment status.

Table 20: Outcome data (FAS, N=377)

	Treatment-naïve N = 206		Previously treated N = 171		Total N = 377	
	BCVA	**CRT**	**BCVA**	**CRT**	**BCVA**	**CRT**
Baseline data available, n (%)	206 (100)	197 (95.6)	171 (100)	165 (96.5)	377 (100)	362 (96.0)
6-month data available, n (%)	125 (60.7)	120 (58.3)	116 (67.8)	111 (64.9)	241 (63.9)	231 (61.3)
12-month data available, n (%)	101 (49.0)	104 (50.5)	93 (54.4)	87 (50.9)	194 (51.5)	191 (50.7)
24-month data available, n (%)	54 (26.2)	53 (25.7)	62 (36.3)	59 (34.5)	116 (30.8)	112 (29.7)

BCVA, best-corrected visual acuity; CRT, central retinal thickness; FAS, full analysis set.

Reference: Tables 2.1.4.1, 2.1.4.2, 4.1.1.1.1, 4.2.2.1.1.1, 4.3.1.1.1, 5.1.1.1, 5.1.3.1 and 5.1.5.1 in Tables Figures and Listings.

10.4 Main results

10.4.1 Change in best-corrected visual acuity

All analyses related to best-corrected visual acuity are detailed in the chapter 4 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Table 21 summarizes BCVA scores at baseline, 6, 12 and 24 months, on the FAS overall and according to the treatment status. Table 22 summarizes the results of the sensitivity analysis performed at 12 months using the missing data imputation via the MCMC method.

For treatment-naïve patients, mean BCVA was significantly improved at 6, 12 and 24 months from baseline ($p<0.001$). At 12 months, mean (±SD) BCVA score was 70.4 (±14.6) letters in treatment-naïve patients and median score reached 73 letters.

For previously treated patients, mean BCVA was significantly improved at 6 and 12 months from baseline ($p<0.001$) but 24-month BCVA was not statistically different from baseline ($p=0.41$). At 12 months, mean (±SD) BCVA score was 64.3 (±17.9) letters in previously treated patients and median score reached 69 letters.

At 12 months, the sensitivity analysis using the missing data imputation via the MCMC method produced similar results to those of the main analysis.

Table 21: BCVA overtime (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
BCVA at baseline, letters count	N	206	171	377
	Mean ± SD	60.8 ± 15.9	58.6 ± 16.7	59.8 ± 16.3
	[95%CI]	[58.6 ; 63.0]	[56.1 ; 61.1]	[58.2 ; 61.5]
	Median	65.0	64.0	65.0
	Q1 ; Q3	52.0 ; 73.0	50.0 ; 69.0	50.0 ; 70.0
	Min ; Max	0 ; 85	0 ; 83	0 ; 85
BCVA at 6 months [a], letters count	N	125	116	241
	Mean ± SD	70.3 ± 13.4	64.9 ± 14.2	67.7 ± 14.0
	p-value*	0.0000	0.0000	0.0000
	[95%CI]	[67.9 ; 72.7]	[62.3 ; 67.5]	[65.9 ; 69.5]
	Median	73.0	69.0	69.0
	Q1 ; Q3	65.0 ; 80.0	58.0 ; 76.0	61.0 ; 77.0
	Min ; Max	8 ; 85	19 ; 85	8 ; 85
BCVA at 12 months [b], letters count	N	101	93	194
	Mean ± SD	70.4 ± 14.6	64.3 ± 17.9	67.5 ± 16.5
	p-value*	0.0000	0.0001	0.0000
	[95%CI]	[67.5 ; 73.3]	[60.7 ; 68.0]	[65.2 ; 69.9]
	Median	73.0	69.0	73.0
	Q1 ; Q3	65.0 ; 80.0	54.0 ; 79.0	60.0 ; 80.0
	Min ; Max	5 ; 85	19 ; 88	5 ; 88
BCVA at 24 months [c], letters count	N	54	62	116
	Mean ± SD	70.3 ± 14.6	62.1 ± 21.3	65.9 ± 18.9
	p-value*	0.0000	0.4153	0.0023
	[95%CI]	[66.3 ; 74.3]	[56.7 ; 67.5]	[62.4 ; 69.4]
	Median	74.5	69.0	70.5
	Q1 ; Q3	65.0 ; 80.0	55.0 ; 76.0	59.5 ; 78.0
	Min ; Max	0 ; 85	0 ; 85	0 ; 85

[a] Patients with BCVA values available at 6 months (i.e. between 4.5 and 6.5 months from first IVT-AFL injection).
[b] Patients with BCVA values available at 12 months (i.e. between 11 and 13 months from first IVT-AFL injection).
[c] Patients with BCVA values available at 24 months (i.e. between 23 and 25 months from first IVT-AFL injection).
* p-value associated with the Student T-test (from baseline).
BCVA, best-corrected visual acuity; CI, confidence interval; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Tables 4.1.1.1.1, 4.1.1.2.1, 4.2.2.1.1 and 4.3.1.1.1 in Tables Figures and Listings.

Table 22: Change in BCVA at 12 months, MCMC imputed results (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
BCVA at baseline, letters count	N	206	171	377
	Mean ± SD	60.8 ± 15.9	58.6 ± 16.7	59.8 ± 16.3
	[95%CI]	[58.6 ; 63.0]	[56.1 ; 61.1]	[58.2 ; 61.5]
	Median	65.0	64.0	65.0
	Q1 ; Q3	52.0 ; 73.0	50.0 ; 69.0	50.0 ; 70.0
	Min ; Max	0 ; 85	0 ; 83	0 ; 85
BCVA at 12 months [a], letters count	N	206	171	377
	Mean ± SD	69.7 ± 14.9	63.1 ± 18.4	66.7 ± 16.9
	[95%CI]	[67.6 ; 71.7]	[60.4 ; 65.9]	[65.0 ; 68.4]
	Median	73.0	68.0	69.9
	Q1 ; Q3	62.8 ; 80.0	53.1 ; 78.0	57.4 ; 79.7
	Min ; Max	5 ; 94	8 ; 103	5 ; 103
Change in BCVA at 12 months [a], letters count	N	206	171	377
	Mean ± SD	8.9 ± 12.9	4.5 ± 11.4	6.9 ± 12.4
	[95%CI]	[7.1 ; 10.6]	[2.8 ; 6.2]	[5.6 ; 8.1]
	Median	8.8	4.4	7.0
	Q1 ; Q3	0.0 ; 16.6	-3.0 ; 12.6	-1.2 ; 15.0
	Min ; Max	-20 ; 58	-31 ; 31	-31 ; 58

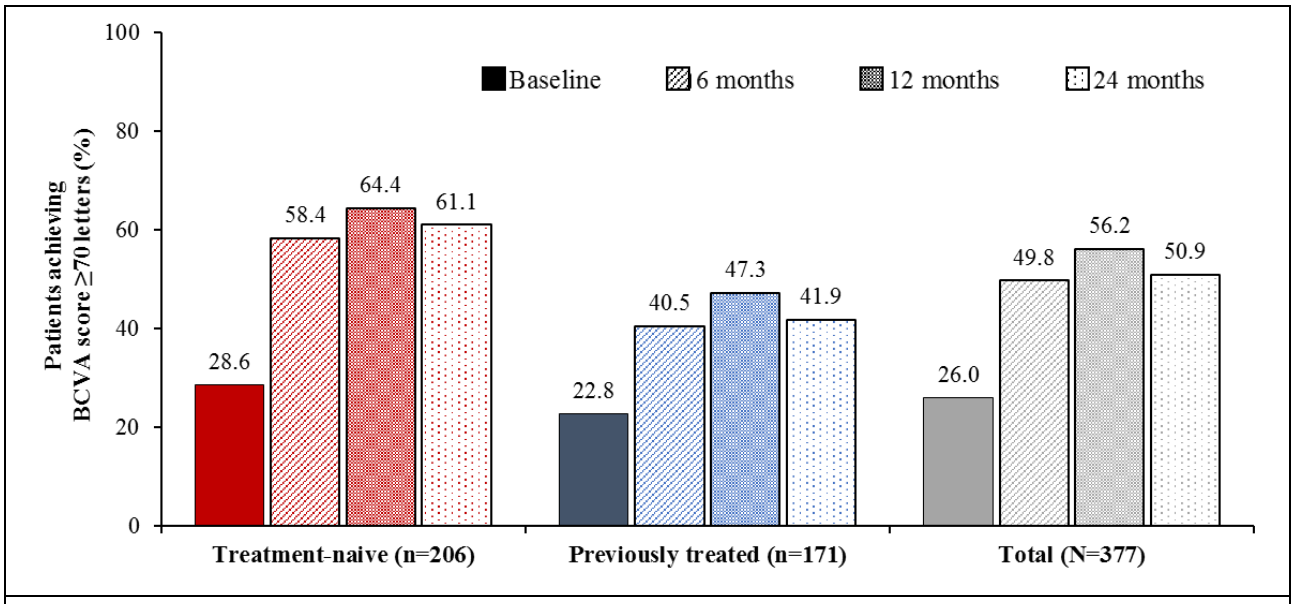
[a] 183 BCVA results missing at 12 months were imputed over the 377 results presented.
BCVA, best-corrected visual acuity; CI, confidence interval; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Table 4.2.1.2.2 in Tables Figures and Listings.

Figure 1 shows the percentage of patients who reached BCVA score ≥70 letters at each timepoint on the FAS overall and according to the treatment status (treatment-naïve and previously treated patients).

The threshold of 70 letters was achieved in 49.8% of the patients (+23.8% from baseline) as early as 6 months. At month 12 and 24, respectively 56.2% and 50.9% of patients achieved BCVA score ≥70 letters. Overall, results were better in treatment-naïve patients compared to previously treated patients.

Figure 1: BCVA ≥70 letters, evolution overtime (FAS, N=377)



BCVA, best-corrected visual acuity; FAS, full analysis set.

Reference: Tables 2.1.4.1, 4.1.1.1.1, 4.2.2.1.1 and 4.3.1.1.1 in Tables Figures and Listings.

Table 23 summarizes the change in BCVA from baseline at 6, 12 and 24 months, on the FAS overall and according to the treatment status. Figure 2 shows mean (±SE) change in BCVA from baseline overtime on the FAS according to the treatment status.

At 12 months, mean (±SD) changes in BCVA were +8.2 (±12.1) letters in treatment-naïve patients and +4.7 (±11.0) letters in previously treated patients. Among treatment-naïve patients, 46.5% have gained at least 2 lines (i.e. +10 letters or more) and 30.7% have gained at least 3 lines (i.e. +15 letters or more). Among previously treated patients, 29.0% have gained at least 2 lines and 16.1% have gained at least 3 lines. Overall, 4.1% of patients have loosed 3 lines or more.

Mean change in BCVA overtime was higher in treatment-naïve patients compared to previously treated patients (see Figure 2).

Table 23: Change in BCVA overtime (FAS, N=377)

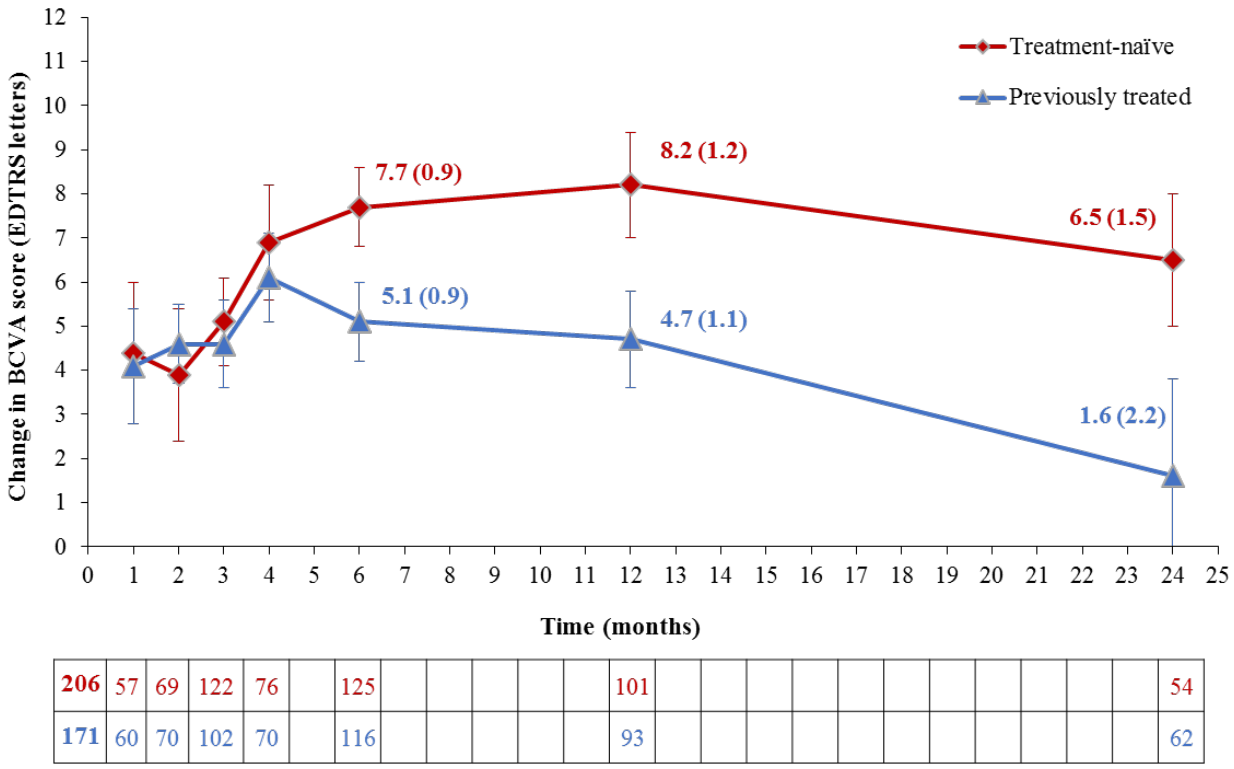
		Treatment-naïve N = 206	**Previously treated N = 171**	**Total N = 377**
BCVA change at 6 months [a], letters count	N	125	116	241
	Mean ± SD	7.7 ± 10.5	5.1 ± 10.1	6.5 ± 10.4
	[95%CI]	[5.9 ; 9.6]	[3.2 ; 6.9]	[5.1 ; 7.8]
	Median	8.0	4.0	6.0
	Q1 ; Q3	1.0 ; 12.0	0.0 ; 11.0	0.0 ; 12.0
	Min ; Max	-45 ; 38	-23 ; 48	-45 ; 48
≤ - 15 letters	n (%)	1 (0.8%)	3 (2.6%)	4 (1.7%)
]-15, - 10] letters	n (%)	2 (1.6%)	3 (2.6%)	5 (2.1%)
]-10, -5] letters	n (%)	6 (4.8%)	9 (7.8%)	15 (6.2%)
]-5, 0[letters	n (%)	10 (8.0%)	12 (10.3%)	22 (9.1%)
[0, 5[letters	n (%)	27 (21.6%)	32 (27.6%)	59 (24.5%)

		Treatment-naïve N = 206	**Previously treated N = 171**	**Total N = 377**
[5, 10[letters	n (%)	30 (24.0%)	21 (18.1%)	51 (21.2%)
[10, 15[letters	n (%)	23 (18.4%)	20 (17.2%)	43 (17.8%)
≥ 15 letters	n (%)	26 (20.8%)	16 (13.8%)	42 (17.4%)
BCVA change at 12 months [b], letters count	N	101	93	194
	Mean ± SD	8.2 ± 12.1	4.7 ± 11.0	6.5 ± 11.7
	[95%CI]	[5.8 ; 10.6]	[2.4 ; 6.9]	[4.8 ; 8.1]
	Median	8.0	5.0	7.0
	Q1 ; Q3	0.0 ; 15.0	-1.0 ; 11.0	0.0 ; 13.0
	Min ; Max	-17 ; 58	-31 ; 31	-31 ; 58
≤ - 15 letters	n (%)	4 (4.0%)	4 (4.3%)	8 (4.1%)
]-15, - 10] letters	n (%)	6 (5.9%)	4 (4.3%)	10 (5.2%)
]-10, -5] letters	n (%)	6 (5.9%)	5 (5.4%)	11 (5.7%)
]-5, 0[letters	n (%)	4 (4.0%)	12 (12.9%)	16 (8.2%)
[0, 5[letters	n (%)	15 (14.9%)	18 (19.4%)	33 (17.0%)
[5, 10[letters	n (%)	19 (18.8%)	23 (24.7%)	42 (21.6%)
[10, 15[letters	n (%)	16 (15.8%)	12 (12.9%)	28 (14.4%)
≥ 15 letters	n (%)	31 (30.7%)	15 (16.1%)	46 (23.7%)
BCVA change at 24 months [c], letters count	N	54	62	116
	Mean ± SD	6.5 ± 10.7	1.6 ± 17.0	3.9 ± 14.6
	[95%CI]	[3.6 ; 9.4]	[-2.7 ; 6.0]	[1.2 ; 6.6]
	Median	7.5	6.5	7.0
	Q1 ; Q3	-3.0 ; 12.0	-4.0 ; 12.0	-4.0 ; 12.0
	Min ; Max	-19 ; 34	-74 ; 30	-74 ; 34
≤ - 15 letters	n (%)	2 (3.7%)	4 (6.5%)	6 (5.2%)
]-15, - 10] letters	n (%)	0 (0.0%)	5 (8.1%)	5 (4.3%)
]-10, -5] letters	n (%)	8 (14.8%)	5 (8.1%)	13 (11.2%)
]-5, 0[letters	n (%)	5 (9.3%)	5 (8.1%)	10 (8.6%)
[0, 5[letters	n (%)	7 (13.0%)	10 (16.1%)	17 (14.7%)
[5, 10[letters	n (%)	10 (18.5%)	12 (19.4%)	22 (19.0%)
[10, 15[letters	n (%)	9 (16.7%)	12 (19.4%)	21 (18.1%)
≥ 15 letters	n (%)	13 (24.1%)	9 (14.5%)	22 (19.0%)

[a] Patients with BCVA values available at 6 months (i.e. between 4.5 and 6.5 months from first IVT-AFL injection).
[b] Patients with BCVA values available at 12 months (i.e. between 11 and 13 months from first IVT-AFL injection).
[c] Patients with BCVA values available at 24 months (i.e. between 23 and 25 months from first IVT-AFL injection).
BCVA, best-corrected visual acuity; CI, confidence interval; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Tables 4.1.1.1.1, 4.2.2.1.1 and 4.3.1.1.1 in Tables Figures and Listings.

Figure 2: Mean change in BCVA overtime (FAS; N=377)



206	57	69	122	76		125						101											54
171	60	70	102	70		116						93											62

Values on the graph are mean (SE). Values in the table are number of patients.
BCVA, best-corrected visual acuity; EDTRS, early treatment diabetic retinopathy study; FAS, full analysis set; SE, standard error..

Reference: Graph 4.4.1 in Tables Figures and Listings

10.4.2 Change in OCT parameters

All analyses related to optical coherence tomography parameters are detailed in the chapter 5 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Table 24Table 21 summarizes CRT at baseline, 6, 12 and 24 months, on the FAS overall and according to the treatment status.

Mean CRT has significantly decreased at 6, 12 and 24 months from baseline (see 95% confidence interval displayed in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Tables 5.1.1.1, 5.1.3.1 and 5.1.5.1). Mean (±SD) CRT were respectively 446.6 (±128.6), 321.3 (±90.2), 315.7 (±101.7) and 312.8 (±93.7) µm at baseline, 6, 12 and 24 months. Results are similar in treatment-naïve and previously treated patients.

Table 24: CRT overtime (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
CRT at baseline [a], µm	N	197	165	362
	Mean ± SD	441.3 ± 122.8	452.9 ± 135.5	446.6 ± 128.6
	Median	423.0	429.0	424.0
	Q1 ; Q3	359.0 ; 514.0	355.0 ; 528.0	355.0 ; 521.0
	Min ; Max	201 ; 933	212 ; 980	201 ; 980
CRT A at 6 months [b], µm	N	120	111	231
	Mean ± SD	317.2 ± 82.3	325.8 ± 98.3	321.3 ± 90.2
	[95%CI]	[302.4 ; 332.1]	[307.3 ; 344.2]	[309.6 ; 333.0]
	Median	302.0	306.0	302.0
	Q1 ; Q3	266.5 ; 353.0	257.0 ; 376.0	259.0 ; 372.0
	Min ; Max	79 ; 697	142 ; 737	79 ; 737
CRT at 12 months [c], µm	N	104	87	191
	Mean ± SD	315.7 ± 95.3	315.6 ± 109.4	315.7 ± 101.7
	[95%CI]	[297.2 ; 334.3]	[292.3 ; 338.9]	[301.2 ; 330.2]
	Median	301.0	294.0	295.0
	Q1 ; Q3	254.0 ; 356.0	249.0 ; 349.0	250.0 ; 350.0
	Min ; Max	151 ; 612	165 ; 789	151 ; 789
CRT at 24 months [d], µm	N	53	59	112
	Mean ± SD	312.3 ± 81.6	313.3 ± 104.1	312.8 ± 93.7
	[95%CI]	[289.8 ; 334.8]	[286.2 ; 340.4]	[295.3 ; 330.4]
	Median	297.0	283.0	286.5
	Q1 ; Q3	264.0 ; 327.0	254.0 ; 340.0	260.0 ; 333.5
	Min ; Max	194 ; 578	172 ; 702	172 ; 702

[a] Patients with CRT values available at baseline
[b] Patients with CRT values available at 6 months (i.e. between 4.5 and 6.5 months from first IVT-AFL injection).
[c] Patients with CRT values available at 12 months (i.e. between 11 and 13 months from first IVT-AFL injection).
[d] Patients with CRT values available at 24 months (i.e. between 23 and 25 months from first IVT-AFL injection).
CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Tables 2.1.4.2, 5.1.1.1, 5.1.3.1 and 5.1.5.1 in Tables Figures and Listings.

Table 25 summarizes the change in CRT from baseline at 6, 12 and 24 months, on the FAS overall and according to the treatment status. Figure 3 shows mean (±SE) change in CRT from baseline overtime on the FAS according to the treatment status. Table 26 summarizes the results of the sensitivity analysis performed at 12 months using the missing data imputation via the MCMC method.

At 12 months, mean (±SD) change in CRT was -124.0 (±149.7) µm. No difference was observed between treatment-naïve and previously treated patients. The sensitivity analysis using the missing data imputation via the MCMC method produced similar results to those of the main analysis.

Table 25: Change in CRT overtime (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
CRT change at 6 months [a], µm	N (missing values)	116 (4)	109 (2)	225 (6)
	Mean ± SD	-121.2 ± 130.3	-115.0 ± 134.6	-118.2 ± 132.1
	[95%CI]	[-145.1 ; -97.2]	[-140.6 ; -89.5]	[-135.6 ; -100.8]
	Median	-87.0	-90.0	-88.0
	Q1 ; Q3	-180.0 ; -36.5	-169.0 ; -27.0	-172.0 ; -31.0
	Min ; Max	-548 ; 165	-591 ; 129	-591 ; 165
CRT change at 12 months [b], µm	N (missing values)	100 (4)	85 (2)	185 (6)
	Mean ± SD	-117.7 ± 144.4	-131.3 ± 156.2	-124.0 ± 149.7
	[95%CI]	[-146.4 ; -89.1]	[-164.9 ; -97.6]	[-145.7 ; -102.2]
	Median	-82.5	-102.0	-88.0
	Q1 ; Q3	-180.0 ; -39.0	-217.0 ; -41.0	-199.0 ; -41.0
	Min ; Max	-577 ; 182	-792 ; 357	-792 ; 357
CRT change at 24 months [c], µm	N (missing values)	51 (2)	58 (1)	109 (3)
	Mean ± SD	-133.7 ± 123.0	-129.8 ± 157.7	-131.6 ± 141.9
	[95%CI]	[-168.3 ; -99.1]	[-171.3 ; -88.3]	[-158.6 ; -104.7]
	Median	-109.0	-113.5	-113.0
	Q1 ; Q3	-217.0 ; -58.0	-221.0 ; -37.0	-217.0 ; -49.0
	Min ; Max	-463 ; 219	-808 ; 214	-808 ; 219

[a] Patients with CRT values available at 6 months (i.e. between 4.5 and 6.5 months from first IVT-AFL injection).
[b] Patients with CRT values available at 12 months (i.e. between 11 and 13 months from first IVT-AFL injection).
[c] Patients with CRT values available at 24 months (i.e. between 23 and 25 months from first IVT-AFL injection).
CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Tables 5.1.1.1, 5.1.3.1 and 5.1.5.1 in Tables Figures and Listings.

Table 26: Change in CRT at 12 months, MCMC imputed results (FAS, N=377)

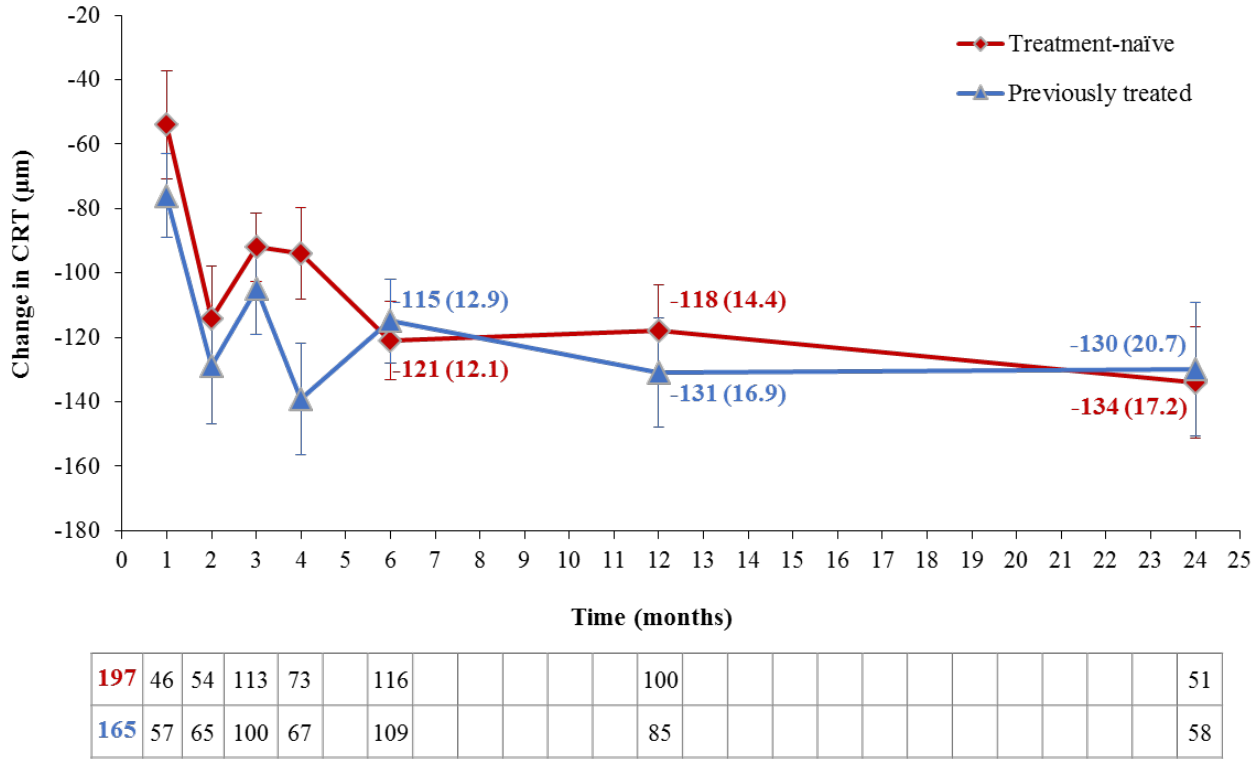
		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
CRT at baseline, µm	N (missing values)	197 (9)	165 (6)	362 (15)
	Mean ± SD	441.3 ± 122.8	452.9 ± 135.5	446.6 ± 128.6
	[95%CI]	[424.1 ; 458.6]	[432.1 ; 473.7]	[433.3 ; 459.9]
	Median	423.0	429.0	424.0
	Q1 ; Q3	359.0 ; 514.0	355.0 ; 528.0	355.0 ; 521.0
	Min ; Max	201 ; 933	212 ; 980	201 ; 980
CRT at 12 months [b], µm	N (missing values)	203 (3)	168 (3)	371 (6)
	Mean ± SD	304.3 ± 92.3	311.4 ± 109.1	307.5 ± 100.2
	[95%CI]	[291.5 ; 317.1]	[294.8 ; 328.0]	[297.3 ; 317.7]
	Median	289.0	296.0	294.0
	Q1 ; Q3	247.0 ; 346.9	242.3 ; 363.4	243.0 ; 353.8
	Min ; Max	84 ; 612	85 ; 789	84 ; 789

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Change in CRT at 12 months [b], µm	N (missing values)	197 (9)	165 (6)	362 (15)
	Mean ± SD	-135.6 ± 150.1	-141.0 ± 143.1	-138.1 ± 146.8
	[95%CI]	[-156.7 ; -114.5]	[-163.0 ; -119.0]	[-153.2 ; -122.9]
	Median	-103.0	-128.6	-116.8
	Q1 ; Q3	-228.3 ; -44.0	-218.3 ; -51.0	-224.4 ; -47.0
	Min ; Max	-792 ; 182	-792 ; 357	-792 ; 357

[a] 180 CRT results missing at 12 months were imputed.
CI, confidence interval; CRT, central retinal thickness; FAS, full analysis set; IVT-AFL, intravitreal aflibercept; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Table 5.1.4.2 in Tables Figures and Listings.

Figure 3: Mean change in CRT overtime (FAS; N=377)



Values on the graph are mean (SE). Values in the table are number of patients.
CRT, central retinal thickness; FAS, full analysis set; SE, standard error.

Reference: Graph 5.2.5.1 in Tables Figures and Listings.

Table 27 summarizes results related to intra-retinal and sub-retinal fluid on OCT at baseline, 6, 12 and 24 months. The percentage of patients with visible intra-retinal fluid on OCT dropped from 96.1% at baseline to 75.4%, 69.3% and 68.8%, respectively at 6, 12 and 24 months. For sub-retinal fluid, the proportion of patients with sub-retinal fluid visible on OCT dropped from 27.7% at baseline to 8.7%, 5.3% and 6.2%, respectively at 6, 12 and 24 months. No significant difference was observed between treatment-naïve and previously treated patients.

Table 27: Visible IRF and SRF on OCT overtime (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
Baseline [a]	N	202	169	371
IRF visible*	n (%)	187 (95.4%)	156 (96.9%)	343 (96.1%)
SRF visible*	n (%)	61 (31.3%)	37 (23.3%)	98 (27.7%)
6 months [b]	N	124	119	243
IRF visible*	n (%)	88 (72.7%)	87 (78.4%)	175 (75.4%)
SRF visible*	n (%)	12 (10.0%)	8 (7.2%)	20 (8.7%)
12 months [c]	N	104	96	200
IRF visible*	n (%)	71 (69.6%)	60 (69.0%)	131 (69.3%)
SRF visible*	n (%)	6 (5.9%)	4 (4.6%)	10 (5.3%)
24 months [d]	N	57	62	119
IRF visible*	n (%)	39 (68.4%)	38 (69.1%)	77 (68.8%)
SRF visible*	n (%)	4 (7.0%)	3 (5.4%)	7 (6.2%)

[a] Patients with OCT performed at baseline.
[b] Patients with OCT performed at 6 months (i.e. between 4.5 and 6.5 months from first IVT-AFL injection).
[c] Patients with OCT performed at 12 months (i.e. between 11 and 13 months from first IVT-AFL injection).
[d] Patients with OCT performed at 24 months (i.e. between 23 and 25 months from first IVT-AFL injection).
*% are calculated based on non-missing data.
FAS, full analysis set; IVT-AFL, intravitreal aflibercept; IRF, intra-retinal fluid; OCT, optical coherence tomography; SRF, sub-retinal fluid.

Reference: Tables 2.1.4..2, 5.1.1.2, 5.1.3.2 and 5.1.5.2 in Tables Figures and Listings.

10.5 Other analyses

10.5.1 DME monitoring

All analyses related to DME monitoring are detailed in the chapter 9 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Table 28 summarizes the number of DME monitoring visits over 6-month, 12-month and 24-month follow-up periods, overall on the FAS and according to the treatment status.

Over the first 6-month follow-up period, the mean (±SD) number of follow-up visits per patient was 6.7 (±1.6). A large majority of the patients (92.0%) performed at least 5 visits and received a mean (± SD) number of 4.9 (±1.4) injections of IVT aflibercept (See Section 10.2.4). No difference was observed between treatment-naïve and previously treated patients.

Over the first 12-month follow-up period, the mean (± SD) number of follow-up visits per patient was 11.4 (±3.0) and the patients received a mean number of 7.3 (±2.6) injections of IVT aflibercept (See Section 10.2.4). More than three quarter of the patients (76.2%) performed at least 10 visits and few patients (3.1%) performed less than 6 visits to their ophthalmologist during the first 12-month observational period.

Over the 24-month follow-up period, the mean (± SD) number of follow-up visits per patient was 19.8 (±5.3) and the patients received a mean number of 11.6 (±4.8) injections of IVT aflibercept (See Section 10.2.4). A large majority of the patients (82.7%) performed at least 15 visits to their ophthalmologist during the first 24-month observational period.

Table 28: DME monitoring visits overtime (FAS, N=377)

		Treatment-naïve N = 206	Previously treated N = 171	Total N = 377
A 6 months [a]	N	182	156	338
Number of follow-up visits per patients	Mean ± SD	6.7 ± 1.7	6.8 ± 1.6	6.7 ± 1.6
	Median	7.0	7.0	7.0
	Q1 ; Q3	6.0 ; 8.0	6.0 ; 8.0	6.0 ; 8.0
	Min ; Max	2 ; 11	2 ; 12	2 ; 12
2 to 4 visits	n (%)	18 (9.9%)	9 (5.8%)	27 (8.0%)
5 to 8 visits	n (%)	144 (79.1%)	129 (82.7%)	273 (80.8%)
>8 visits	n (%)	20 (11.0%)	18 (11.5%)	38 (11.2%)
At 12 months [b]	N	149	141	290
Number of follow-up visits per patients	Mean ± SD	11.3 ± 2.9	11.6 ± 3.1	11.4 ± 3.0
	Median	12.0	12.0	12.0
	Q1 ; Q3	10.0 ; 13.0	10.0 ; 13.0	10.0 ; 13.0
	Min ; Max	2 ; 17	5 ; 21	2 ; 21
<6 visits	n (%)	6 (4.0%)	3 (2.1%)	9 (3.1%)
6 to 9 visits	n (%)	28 (18.8%)	32 (22.7%)	60 (20.7%)
>9 visits	n (%)	115 (77.2%)	106 (75.2%)	221 (76.2%)
At 24 months [c]	N	79	89	168
Number of follow-up visits per patients	Mean ± SD	19.4 ± 4.7	20.2 ± 5.8	19.8 ± 5.3
	Median	19.0	20.0	20.0
	Q1 ; Q3	17.0 ; 23.0	16.0 ; 24.0	16.5 ; 23.0
	Min ; Max	4 ; 28	7 ; 33	4 ; 33
<10 visits	n (%)	2 (2.5%)	3 (3.4%)	5 (3.0%)
10 to 15 visits	n (%)	12 (15.2%)	12 (13.5%)	24 (14.3%)
>15 visits	n (%)	65 (82.3%)	74 (83.1%)	139 (82.7%)

[a] Patients followed at least 4.5 months.
[b] Patients followed at least 11 months.
[c] Patients followed at least 23 months.
DME, diabetic macular edema; FAS, full analysis set; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Reference: Table 9.1 in Tables Figures and Listings.

10.5.2 Change in FA / FP parameters

All analyses related to fluorescein angiography and fundus photography parameters are detailed in the chapter 6 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Data related to the change in FA parameters at 24 months from baseline are displayed in Table 6.1 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents, overall on the FAS and according to the treatment status. The number of available assessments at 24 months is too small (2 patients) and does therefore not allow any relevant analysis.

Data related to the change in FP parameters at 24 months from baseline are displayed in Table 6.2 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents, overall on the FAS and according to the treatment status. Overall, data from 82 patients (41 treatment-naïve patients and 41 previously treated patients) were analyzed. The results show a reduction of some anatomical abnormalities associated with the DME (intra-retinal microvascular abnormalities, microaneurysms and hemorrhages, hard and soft exudates, neovascularization of the disc, new vessels) between baseline and 24 months, but the number of available data is insufficient to produce robust analyses on these parameters. No difference was observed between treatment-naïve and previously treated patients.

10.5.3 Change in glycaemia and HbA1c level

All analyses related to glycemia and glycated hemoglobin are detailed in the chapter 8 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Data related to the change in glycemia at 6, 12 and 24 months from baseline are displayed in Table 8.1 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents, overall on the FAS and according to the treatment status. Very few data were routinely collected during the follow-up period, and thus did not allow any relevant analysis on the available data.

Data related to the change in glycated hemoglobin (HbA1c) at 6, 12 and 24 months from baseline are displayed in Table 8.2 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents, overall on the FAS and according to the treatment status. The results did not show any significant change HbA1c level overtime.

10.5.4 Change in blood pressure

All analyses related to blood pressure are detailed in the chapter 7 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Data related to the change in diastolic and systolic blood pressure at 6, 12 and 24 months from baseline are displayed in Tables, Figures and Listings in Annex 1: List of stand-alone documents Tables 7.1 and 7.2, overall on the FAS and according to the treatment status. The results did not show any significant change in blood pressure overtime.

10.5.5 Switched patients

Additional post-hoc analyses on switched patients (i.e. patients who discontinued the study prematurely to switch to another DME treatment) are detailed in the chapter 12 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

Data are displayed in Table 12.1.1 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents, overall on the FAS and according to the treatment status. Out of the 57 patients recorded as “switched patient” in the study, 29 (50.9%) were treatment-naïve patients and 28 (49.1%) were previously treated patients. Overall, the mean (±SD) change in BCVA before switch was 0.8 (±13.2) letters and 68.0% of the patients had recorded no improvement or a decrease in visual acuity before switching. No difference was observed between treatment-naïve and previously treated patients. Of note, only 25 (43.9%) patients had a BCVA available before the switch (i.e. within 2 months before the switch) and results must therefore be interpreted with caution.

10.6 Adverse events/adverse reactions

All analyses related to adverse events are detailed in the chapter 10 of the Tables, Figures and Listings (see Annex 1: List of stand-alone documents.

10.6.1 Brief summary of adverse events

Overall summaries of ocular and non-ocular TEAEs are presented in Table 29 overall on the SAS and according to the treatment status.

Three-hundred and eighty-nine patients compose the safety analysis set (SAS) and recorded, 1917 TEAEs within the study period.

In regards to the ocular TEAEs, 252 (64.8%) patients experienced 954 ocular TEAEs. Out of them, 53 (13.6%) patients experienced 111 ocular TEAEs related to procedure, mainly (109 TEAEs, 98.2%) non serious TEAEs, 19 (4.9%) patients experienced 21 treatment-related ocular TEAEs (excluding off-label use TEAEs), mainly (19 TEAEs, 90.5%) non serious treatment-related TEAEs and 5 (1.3%) patients experienced 5 non-serious ocular TEAEs that led to treatment discontinuation. Overall, 14 (3.6%) patients experienced 18 serious ocular TEAEs, out of which 2 (11.1%) were related to procedure, 2 (11.1%) were related to treatment and 14 (77.8%) were unrelated to procedure or treatment.

In regards to the non-ocular TEAEs, 214 (55.0%) patients experienced 963 non-ocular TEAEs. Out of them, 15 (3.9%) patients experienced 58 non serious TEAEs related to procedure, 7 (1.8%) patients experienced 8 treatment-related TEAEs, mainly (6 TEAEs, 75.0%) non serious treatment-related TEAEs and 4 (1.0%) patients experienced 4 TEAEs that led to treatment discontinuation, mainly (3 TEAEs, 75%) non serious TEAEs. Overall, 70 (18.0%) patients experienced 193 serious non-ocular TEAEs out of which 2 (1.0%) were related to treatment, none was related to procedure and 191 (99.0%) were unrelated to procedure or treatment.

Eight (2.1%) patients died during the study, but none of TEAEs leading to death was related to the study drug or IVT injection procedure (see Tables, Figures and Listings in Annex 1: List of stand-alone documents Listing 10.1.4).

Overall, 1109 (57.9%) "off-label use" TEAEs (653 [58.9%] ocular TEAE and 456 [41.2%] non-ocular TEAE) were recorded in 251 (64.5%) patients. These “off-label use” TEAE were mainly inappropriate schedule of product/drug administration (See Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listings 10.1.1 and 10.1.8).

Table 29: Overview of TEAEs (SAS, N=389)

		Treatment-naïve N = 211	Previously treated N = 177	Total N = 389*
Any ocular TEAE‡	**n (%) [e]**	**126 (59.7%) [427]**	**126 (71.2%) [527]**	**252 (64.8%) [954]**
Serious TEAE	n (%) [e]	9 (4.3%) [12]	5 (2.8%) [6]	14 (3.6%) [18]
Treatment-related TEAE†	n (%) [e]	8 (3.8%) [9]	11 (6.2%) [12]	19 (4.9%) [21]
Serious treatment-related TEAE	n (%) [e]	0 (0.0%) [0]	2 (1.1%) (2]	2 (0.5%) [2]
TEAE related to procedure	n (%) [e]	23 (10.9%) [40]	30 (16.9%) [71]	53 (13.6%) [111]
Serious TEAE related to procedure	n (%) [e]	1 (0.5%) [1]	1 (0.6%) [1]	2 (0.5%) [2]
TEAE leading to IVT-AFL discontinuation	n (%) [e]	4 (1.9%) [4]	1 (0.6%) [1]	5 (1.3%) [5]
Serious TEAE leading to IVT-AFL withdrawal	n (%) [e]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]
Any non-ocular TEAE§	**n (%) [e]**	**111 (52.6%) [521]**	**103 (58.2%) [442]**	**214 (55.0%) [963]**
Serious TEAE	n (%) [e]	43 (20.4%) [112]	27 (15.3%) [81]	70 (18.0%) [193]
Treatment-related TEAE†	n (%) [e]	2 (0.9%) [2]	5 (2.8%) [6]	7 (1.8%) [8]
Serious treatment-related TEAE	n (%) [e]	0 (0.0%) [0]	1 (0.6%) [2]	1 (0.3%) [2]
TEAE related to procedure	n (%) [e]	7 (3.3%) [25]	8 (4.5%) [33]	15 (3.9%) [58]
Serious TEAE related to procedure	n (%) [e]	0 (0.0%) [0]	0 (0.0%) [0]	0 (0.0%) [0]
TEAE leading to IVT-AFL discontinuation	n (%) [e]	2 (0.9%) [2]	2 (1.1%) [2]	4 (1.0%) [4]
Serious TEAE leading to IVT-AFL withdrawal	n (%) [e]	1 (0.5%) [1]	0 (0.0%) [0]	1 (0.3%) [1]
TEAE leading to death	n (%) [e]	4 (1.9%) [4]	4 (2.3%) [6]	8 (2.1%) [10]

*One patient has no treatment status defined but did not experienced any TEAE. †Excluding "off-label use" TEAE. ‡Including 653 "off-label use" TEAEs recorded in 166 subjects. §Including 456 "off-label use" TEAEs recorded in 132 subjects.
e, number of adverse events; IVT-AFL, intravitreal aflibercept; n(%), number of subjects (percentage of subject); SAS, safety analysis set; TEAE, treatment-emergent adverse event

Reference: Tables 10.1.1 and 10.1.2 in Tables Figures and Listings.

10.6.2 Treatment-emergent adverse events

Table 30 summarizes ocular TEAEs by preferred term on the SAS overall and according to the treatment status.

The most frequently reported ocular TEAEs was cataract (33 patients, 8.5%). Most ocular TEAEs were reported with a PT incidence ≤2% (see Tables, Figures and Listings in Annex 1: List of stand-alone documents, Table 10.1.3).

Table 30: Ocular TEAE frequency by PT (SAS, N=389)

		Treatment-naïve N = 211	Previously treated N = 177	Total N = 389*
Any ocular TEAE	**n (%)**	**126 (59.7%)**	**126 (71.2%)**	**252 (64.8%)**
Ocular TEAE >2%‡				
[Cataract]	n (%)	12 (5.7%)	21 (11.9%)	33 (8.5%)
[Diabetic retinal oedema]	n (%)	12 (5.7%)	13 (7.3%)	25 (6.4%)
[Visual acuity reduced]	n (%)	6 (2.8%)	10 (5.6%)	16 (4.1%)
[Macular oedema]	n (%)	11 (5.2%)	4 (2.3%)	15 (3.9%)
[Lacrimation increased]	n (%)	7 (3.3%)	1 (0.6%)	8 (2.1%)
[Ocular hypertension]	n (%)	2 (0.9%)	6 (3.4%)	8 (2.1%)
[Vitreous floaters]	n (%)	6 (2.8%)	2 (1.1%)	8 (2.1%)
[Dry eye]	n (%)	1 (0.5%)	5 (2.8%)	6 (1.5%)
[Posterior capsule opacification]	n (%)	2 (0.9%)	4 (2.3%)	6 (1.5%)
[Vision blurred]	n (%)	5 (2.4%)	0 (0.0%)	5 (1.3%)

*One patient has no treatment status defined but did not experienced any TEAE. ‡TEAE occurred at a frequency >2% (excluding off-label use TEAEs) in at least one subgroup (treatment-naïve or previously treated).
PT, preferred term; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

Reference: Table 10.1.3 in Tables Figures and Listings.

Table 31 summarizes non-ocular TEAEs by preferred term on the SAS overall and according to the treatment status.

The most frequently reported non-ocular TEAEs were bronchitis (9 patients, 2.3%) and hypertension (8 patients, 2.1%). Most non-ocular TEAEs were reported with a PT incidence ≤2% (see Tables, Figures and Listings in Annex 1: List of stand-alone documents, Table 10.1.3).

Table 31: Non-ocular TEAE frequency by PT (SAS, N=389)

		Treatment-naïve N = 211	Previously treated N = 177	Total N = 389*
Any non-ocular TEAE	**n (%)**	**111 (52.6%)**	**103 (58.2%)**	**214 (55.0%)**
Non-ophthalmological TEAE >2%‡				
[Bronchitis]	n (%)	4 (1.9%)	5 (2.8%)	9 (2.3%)
[Hypertension]	n (%)	5 (2.4%)	3 (1.7%)	8 (2.1%)

*One patient has no treatment status defined but did not experienced any TEAE. ‡TEAE occurred at a frequency >2% (excluding off-label use TEAEs and diabetes mellitus) in at least one subgroup (treatment-naïve or previously treated).
PT, preferred term; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

Reference: Table 10.1.3 in Tables Figures and Listings.

Table 32 summarizes treatment-related TEAEs by system organ class and preferred term on the SAS overall and according to the treatment status.

The most frequently reported treatment-related AEs belong to eye disorders SOC (11 patients, 2.8%, 13 TEAEs). All other SOC occurred at an incidence <2.0% and no individual treatment-related TEAE occurred with a PT incidence >1.7%.

Table 32: Treatment-related TEAE frequency by SOC [PT] (SAS, N=389)

		Treatment-naïve N = 211	Previously treated N = 177	Total N = 389*
Any treatment-related TEAE‡	**n (%)**	**10 (4.7%)**	**16 (9.0%)**	**26 (6.7%)**
Eye disorders	n (%)	3 (1.4%)	8 (4.5%)	11 (2.8%)
[Visual acuity reduced]	n (%)	1 (0.5%)	3 (1.7%)	4 (1.0%)
[Conjunctival haemorrhage]	n (%)	0 (0.0%)	2 (1.1%)	2 (0.5%)
[Diabetic retinal oedema]	n (%)	2 (0.9%)	0 (0.0%)	2 (0.5%)
[Cystoid macular oedema]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Lacrimation increased]	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
[Maculopathy]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Photopsia]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Vitreous detachment]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
General disorders and administration site conditions	n (%)	4 (1.9%)	3 (1.7%)	7 (1.8%)
[Drug ineffective]	n (%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
[Injection site pain]	n (%)	1 (0.5%)	1 (0.6%)	2 (0.5%)
[Injection site pruritus]	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
[Therapeutic product ineffective]	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Cardiac disorders	n (%)	1 (0.5%)	1 (0.6%)	2 (0.5%)
[Angina pectoris]	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
[Coronary artery stenosis]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Injury, poisoning and procedural complications	n (%)	0 (0.0%)	2 (1.1%)	2 (0.5%)
[Incorrect dose administered]	n (%)	0 (0.0%)	2 (1.1%)	2 (0.5%)
Gastrointestinal disorders	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
[Dyspepsia]	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Infections and infestations	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Endophthalmitis]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Metabolism and nutrition disorders	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
[Hypovitaminosis]	n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Skin and subcutaneous tissue disorders	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Skin reaction]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)

*One patient has no treatment status defined but did not experienced any TEAE. ‡Excluding off-label use TEAEs.
PT, preferred term; SAS, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Reference: Table 10.1.5 in Tables Figures and Listings.

10.6.3 Death and other serious adverse events

All data regarding serious TEAEs (including TEAEs leading to death) are displayed in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Tables 10.1.4 and 10.1.6 and in Listings 10.1.3, 10.1.4 and 10.1.6.

Eight (2.1%) patients died during the study but none of the AE that led to death was considered to be related to the study drug. Details of the 10 TEAEs that led to death are provided in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listing 10.1.4.

Table 33 summarizes serious TEAEs (including TEAEs that led to death) by system organ class and preferred term on the SAS overall and according to the treatment status.

Overall, 84 (21.6%) patients experienced 211 serious TEAEs (See Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listing 10.1.3). The most frequently reported serious AEs belong to cardiac disorders SOC (20 patients, 5.1% overall and 5.6% in previously treated patients) and surgical and medical procedures (15 patients, 3.9% overall and 5.2% in treatment-naïve patients). All other SOC occurred at an incidence <5% and no individual serious TEAE occurred with a PT incidence >1.4%.

Table 33: Serious TEAE frequency by SOC [PT] (SAS, N=389)

		Treatment-naïve N = 211	Previously treated N = 177	Total N = 389*
Any serious TEAE‡	**n (%)**	**52 (24.6%)**	**32 (18.1%)**	**84 (21.6%)**
Serious TEAE >1%§				
Cardiac disorders	n (%)	10 (4.7%)	10 (5.6%)	20 (5.1%)
[Acute coronary syndrome]	n (%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
[Myocardial infarction]	n (%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
Surgical and medical procedures	n (%)	11 (5.2%)	4 (2.3%)	15 (3.9%)
[Drug delivery device implantation]	n (%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
[Knee arthroplasty]	n (%)	0 (0.0%)	2 (1.1%)	2 (0.5%)
Metabolism and nutrition disorders	n (%)	9 (4.3%)	5 (2.8%)	14 (3.6%)
Renal and urinary disorders	n (%)	7 (3.3%)	6 (3.4%)	13 (3.3%)
[Acute kidney injury]	n (%)	3 (1.4%)	2 (1.1%)	5 (1.3%)
Eye disorders	n (%)	7 (3.3%)	4 (2.3%)	11 (2.8%)
[Retinal detachment]	n (%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
Injury, poisoning and procedural complications	n (%)	9 (4.3%)	2 (1.1%)	11 (2.8%)
Nervous system disorders	n (%)	7 (3.3%)	3 (1.7%)	10 (2.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	n (%)	3 (1.4%)	5 (2.8%)	8 (2.1%)
Infections and infestations	n (%)	3 (1.4%)	4 (2.3%)	7 (1.8%)
[Erysipelas]	n (%)	1 (0.5%)	2 (1.1%)	3 (0.8%)
Respiratory, thoracic and mediastinal disorders	n (%)	3 (1.4%)	3 (1.7%)	6 (1.5%)
[Acute pulmonary oedema]	n (%)	1 (0.9%)	2 (1.1%)	3 (1.0%)
Gastrointestinal disorders	n (%)	4 (1.9%)	2 (1.1%)	6 (1.5%)
Vascular disorders	n (%)	4 (1.9%)	2 (1.1%)	6 (1.5%)
General disorders and administration site conditions	n (%)	1 (0.5%)	4 (2.3%)	5 (1.3%)
Musculoskeletal and connective tissue disorders	n (%)	3 (1.4%)	1 (0.6%)	4 (1.0%)

*One patient has no treatment status defined but did not experienced any TEAE. ‡Excluding off-label used TEAE.
§TEAE occurred at a frequency >1% (excluding diabetes mellitus) in at least one subgroup (treatment-naïve or previously treated).
PT, preferred term; SAS, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Reference: Table 10.1.4 in Tables Figures and Listings.

Table 34 summarizes serious treatment-related TEAEs by system organ class and preferred term on the SAS overall and according to the treatment status.

Overall, 3 patients (all previously treated patients) experienced each one serious treatment-related TEAE during the course of the study. Coronary artery stenosis occurred in a PPD subject approximately one month after the first IVT aflibercept injection; the AE was resolved 7 days later

and treatment with IVT aflibercept was not interrupted. Vitreous detachment occurred in a PPD subject approximately 3 months after the first ICT aflibercept injection; the AE was resolved with sequelae and did not led to any treatment interruption. Endophthalmitis in study eye occurred in a PPD subject approximately 10 months after IVT aflibercept initiation and led to treatment interruption; infection was resolving at the last contact. Details on these TEAEs are displayed in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listing 10.1.6.

Table 34: Serious treatment-related TEAE frequency by SOC [PT] (SAS, N=389)

		Treatment-naïve N = 211	Previously treated N = 177	Total N = 389*
Any serious treatment-related TEAE‡	**n (%)**	**0 (0.0%)**	**3 (1.7%)**	**3 (0.8%)**
Cardiac disorders	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Coronary artery stenosis]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Eye disorders	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Vitreous detachment]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
Infections and infestations	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
[Endophthalmitis]	n (%)	0 (0.0%)	1 (0.6%)	1 (0.3%)

*One patient has no treatment status defined but did not experienced any TEAE. ‡Excluding off-label used TEAE.
PT, preferred term; SAS, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Reference: Table 10.1.6 in Tables Figures and Listings.

10.6.4 Adverse events leading to discontinuation and other significant adverse events

Overall, 9 (2.3%) patients experienced an AE that led to IVT aflibercept permanent discontinuation, mainly drug ineffective to improve diabetic retinal edema (3 patients). None of these TEAE occurred with a PT incidence >1%. Details related to these TEAEs are provided in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Table 10.1.7.

During the study, 73 (18.8%) patients experienced 105 TEAEs requiring special attention (as defined in RMP), i.e. endophthalmitis (likely infectious origin) or intraocular inflammation or transient intraocular pressure increase, or retinal pigment epithelial tears or retinal tear / detachment or cataract (especially of traumatic origin) or hypersensitivity and immunogenicity or arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events, or venous thromboembolic events or hypertension or proteinuria or non-ocular hemorrhage or retinal hemorrhage or embryo-fetotoxicity. The most frequently reported TEAEs belong to the eye disorders SOC (79 TEAEs, mainly cataract). Details of all 105 TEAEs requiring special attention are displayed in Tables, Figures and Listings in Annex 1: List of stand-alone documents, Listing 10.1.7. No safety signal was detected from this Listing.

10.6.5 Non treatment-emergent adverse events

Non treatment-emergent adverse events are events reported in the eCRF that occurred before the first IVT aflibercept injection or more than 30 days after the last IVT aflibercept injection (see definition provided in Section 9.9.2.7).

Overall, 16 (4.1%) patients experienced 26 AEs not treatment-emergent, and all of them but two occurred more than 30 days after the last IVT aflibercept injection. Details related to these AEs are displayed in Tables, Figures and Listings in Annex 1: List of stand-alone documents Listing 10.1.9.

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 EYLEA® in routine clinical practice in France and also to describe the condition of use of EYLEA® in real-conditions settings.

Three-hundred and seventy-seven patients were analyzed through this study, 206 of whom were treatment-naïve patients (i.e. patients not previously treated with an anti-VEGF agent, intra-ocular steroids or laser in the study eye, and not previously treated with an anti-VEGF agent or intra-ocular steroids in the fellow eye) and the 171 remaining were previously treated patients. Patients had mean (±SD) age of 65.9 (±11.1) years (range, 19-91 years) and most of them were followed for their diabetes for more than 10 years. Median time since DME diagnosis was about 1 month in treatment-naïve patients vs. 28 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 59.8 (±16.3) letters, and mean (±SD) CRT was 447 (±129) µm.

Over the first 6-month follow-up period, patients had a mean (±SD) of 6.7 (±1.6) visits referring to study eye during which they received a mean (±SD) of 4.9 (±1.4) IVT aflibercept injections. Over the first 1-year follow-up period, patients had mean (±SD) of 11.4 (±3.0) visits referring to study eye and received a mean (±SD) of 7.3 (±2.6) IVT aflibercept injections. These figures highlight a good compliance with administration scheme, especially regarding the loading dose. For the subjects who have been followed for 2 years, they had a mean (±SD) of 19.8 (±5.3) follow-up visits which underlines the good monitoring (on a monthly basis) of these DME patients in routine practice in France.

The evolution of BCVA and CRT over the first 1-year follow-up indicates 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 letters vs. +5.0 in previously treated patients). This important improvement in treatment-naïve patients at 12 months is also illustrated by the proportion of patients who achieved the patient beneficial threshold of 70 letters for BCVA assessment which increased by 35% compared to 24% in previously treated patients. Additionally, the rate of 31% of treatment-patients who obtained a gain of at least 3 lines (i.e. ≥+15 letters) is also indicative of the very good results observed in these subjects (vs. 16% among previously treated patients). As regards CRT results, treatment-naïve and previously treated patients had similar CRT before the first IVT aflibercept injection (i.e. 446.6 ±128.6 µm) which suggest that previous DME treatment did not significantly improve anatomic parameters while IVT aflibercept treatment significantly reduced edema in both subgroups (CRT decreased by -124.0 ±149.7 µm from baseline). In addition, the significant reduction in the rate of patients with intra and sub-retinal fluid visible at OCT (-25% and -20% from baseline, respectively) attests to the impact of treatment on anatomical parameters. The sensitivity analysis using multiple imputation method produced identical results to the main analysis and thus confirm the validity of the results observed on the full analysis

set. These results are also confirmed at 24 months with a long term improvement of BCVA (median change of +7.5 letters and +6.5 letters, respectively in treatment-naïve and previously treated patients) and CRT (CRT decreased by -131.6 ±141.9 µm from baseline).

Safety results are common to the known safety profile observed in RCT. No new safety signal has been identified in this analysis. Among the study population, 26 (6.7%) patients experienced adverse event possibly related to EYLEA®, and only 3 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. In order to provide relevant analysis at each timepoint, time windows were within the statistical analysis plan; thus, 6-months data are data assessed within the time frame of [4.5-6.5[months from the first IVT aflibercept injection, 12-month data are data assessed within the time frame of [11-13] months from the first IVT aflibercept injection and 24-months data are data assessed within the time frame of [23-25] months from the first IVT aflibercept injection.

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, sensitivity analyses were conducted to impute missing BCVA and CRT values. Two imputation methods were used: median imputation and multiple imputation using Markov Chain Monte Carlo (MCMC). When there is few missing data (i.e. <20%), simple imputation methods (e.g. median imputation) can be applied. When there are more missing data (i.e. up to 50%), more sophisticated methods, with modelling, continue to have good results. This is particularly the case with multiple imputations which is a relatively flexible and increasingly popular approach to dealing with missing data (12, 13). Another disadvantage of simple imputation methods, especially when the number of missing data is large, is that these methods may underestimate the standard error by ignoring the uncertainty of the imputed data. This may lead to confidence intervals for the estimation of the treatment effect that may be too narrow and give a wrong impression of accuracy that does not really exist. Considering the rate of missing data observed at 12 months within the APOLLON study (48.5% for BCVA and 49.3% for CRT), the median imputation is not appropriate and only multiple imputation methods should be considered. The validity of the multiple imputation method (with the MCMC method) was verified by analyzing the missing data profile of the variables concerned (BCVA and CRT). The analysis revealed a pattern of arbitrary data that therefore validates the possibility of using the multiple imputation method to test the robustness of the main analysis (14).

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, 5, 15-17), but none of them has provided real word data for IVT aflibercept. 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 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, with a mean number of 4.9 IVT aflibercept injections over the first 6 months and 7.7 IVT aflibercept injections over the first year of treatment.

The main results from VIVID study after 12 and 24 months follow-up are summarized in Table 35 and Table 36.

Table 35: Comparison to VIVID study / 12 months follow-up

	APOLLON RWE Treatment-naïve patients N = 101*	**VIVID (4)** RCT 2q8 arm Treatment-naïve patients N = 135
	aflibercept	aflibercept
Mean baseline BCVA (letters)	62.3	58.8
Mean 12-month BCVA (letters)	70.4	69.5
Mean BCVA gain (letters)	+8.2	+10.7
Mean number of injections	7.7	8.7
Gain ≥2 lines (%)	47.0	53.3
Gain ≥3 lines (%)	31.0	33.3
12-month BCVA ≥70 letters (%)	64.4	Not available

*at 12 months, 101 patients (out of the 206 from the treatment-naïve subgroup) had BCVA data available.
2q8, 2 mg every 8 weeks; BCVA, best-corrected visual acuity; RCT, randomized controlled trial; RWE, real world evidence.

Table 36: Comparison to VIVID study / 24 months follow-up

	APOLLON RWE Treatment-naïve patients N = 54*	**VIVID (5, 17)** RCT 2q8 arm Treatment-naïve patients N = 135
	aflibercept	aflibercept
Mean baseline BCVA (letters)	63.8	58.8
Mean 24-month BCVA (letters)	70.3	68.2
Mean BCVA gain (letters)	+6.5	+9.4
Mean number of injections	11.8	13.6
Gain ≥2 lines (%)	41.0	49.6
Gain ≥3 lines (%)	24.0	31.1
24-month BCVA ≥70 letters (%)	61.1	Not available

*at 24 months, 54 patients (out of the 206 from the treatment-naïve subgroup) had BCVA data available.
2q8, 2 mg every 8 weeks; BCVA, best-corrected visual acuity; RCT, randomized controlled trial; RWE, real world evidence.

11.4 Generalizability

The study was conducted in DME patients and as described in Section 10.2, baseline characteristics of treatment-naïve and previously treated patients reflect that seen in real-conditions settings in US (18). Moreover, most patient were treated according to the current recommendation regarding the number of IVT aflibercept injections received and DME monitoring, which suggest no major bias as regards treatment administration. Results observed through this 2-years follow-up study may therefore reflect those observed in DME patients in real-conditions settings.

12. Other information

Not applicable.

13. Conclusion

The APOLLON study showed that IVT aflibercept was associated with visual and anatomical improvements in patients with DME in routine clinical practice in France.

Treatment with IVT aflibercept resulted in a long term BCVA improvement with a mean gain at 12 months of 8.2 letters for treatment-naïve and 4.7 letters for previously treated patients, respectively. The 70 letters threshold was reached by 56% of the patients, and 24% achieved a gain of at least 3 lines. Macular edema was also reduced in both subgroups (CRT decrease by 124 µm). 24-month results also confirm the positive impact of IVT aflibercept in DME patients, especially in treatment-naïve patients.

The APOLLON study also highlights the good DME management in routine clinical practice in France with a mean number of 4.9 IVT aflibercept injections over the first 6 months and 7.3 injections over the first 12 months. Patients were mainly followed on a monthly basis and injection scheme was compliant with the current recommendations (i.e. loading dose to be injected during the first 6 months of treatment).

No new safety profile has been observed with 6.7% of patients having experienced an EYLEA® related adverse event and 0.8% having experienced a serious EYLEA® related adverse event.

Overall, efficacy and safety results observed in the APOLLON study are consistent with those reported in randomized studies of patients with DME.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 37: List of stand-alone documents

Document Name	Final version and date (if available)*
18636_APOLLON_List of investigators	02 JUL 2018
18636_APOLLON_Steering committee members	02 DEC 2015
18636_APOLLON_Study protocol	Version 2.0 dated 13 JAN 2017
18636_APOLLON_CRF	Version 6.0 dated 15 MAY 2017
18636_DMP/DMR	Version 6.0 dated 27 DEC 2019
18636_APOLLON_QRP	Version 3.0 dated 04 JAN 2019
18636_APOLLON_FR_SAP	Version 5.0 dated 11 NOV 2019
18636_APOLLON_Global Monitoring Report	Version 1.0 dated 24 FEB 2020
18636_APOLLON_Table Figures Listings	Version 2.0 dated 03 JUL 2020

Annex 2: Additional information

Not applicable.

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 – 06 JUL 2020
IMPACT study number	18636
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
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: PPD

Date, Signature: 21/July/2020, PPD

Signature Page – OS Conduct Responsible

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 – 06 JUL 2020
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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: PPD

Date, Signature: Loos le 21/07/2020, PPD

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
Report version and date	Version 1.0 – 06 JUL 2020
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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: PPD

Date, Signature: 21 juillet 2020 PPD

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 – 06 JUL 2020
IMPACT study number	18636
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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: PPD

Date, Signature: 21 JUL 2020, PPD

Signature Page – OS Global 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
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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: PPD PPD

Date, Signature: 22-JUL-2020, _____

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
Report version and date	Version 1.0 – 06 JUL 2020
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Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
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: PPD

Date, Signature: 07/07/2020, PPD

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
Report version and date	Version 1.0 – 06 JUL 2020
IMPACT study number	18636
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
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: PPD

Date, Signature: 07-Jul-2020 PPD