Clinical Study Synopsis

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1. Abstract

Acronym/Title	APOLLON – A prospective observational study conducted in France to describe routine clinical practice for treatment-naïve or previously treated patients with diabetic macular edema (DME) who are starting 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.