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ORIGINAL RESEARCH

Dosing Regimens of Intravitreal Aflibercept for Diabetic Macular Edema Beyond the First Year: VIOLET, a Prospective Randomized Trial

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ABSTRACT

Introduction: The purpose was to compare two flexible regimens of intravitreal aflibercept (IVT-AFL) with fixed dosing every 8 weeks, beyond the first year of treatment, in patients with diabetic macular edema (DME). VIOLET was a 100-week, randomized, Phase IIIb, non-inferiority study in patients with center-involving DME previously treated with IVT-AFL for ≥ 1 year according to the European label.

Methods: Patients received an initial dose of IVT-AFL at study baseline and were randomly assigned (1:1:1) to treat-and-extend (T&E), pro re nata (PRN), or fixed regimens. The primary endpoint was mean change in best-corrected visual acuity

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(BCVA) from baseline (randomization) to Week 52.
Results: Full analysis set comprised 458 patients (baseline mean BCVA: 72.5, 71.0, and 72.7 letters in the T&E, PRN, and fixed-dose groups, respectively). Patients received a mean (min–max) of 10.0 (2–14; T&E), 11.5 (1–25; PRN), and 12.3 (3–13; fixed) injections over 100 weeks, with 13.3 (4–23), 25.0 (3–29), and 16.1 (5–25) clinic visits, respectively. At Week 52, mean (± standard deviation) BCVA changes from baseline were + 0.5 ± 6.7 (T&E), + 1.7 ±6.8 (PRN), and + 0.4 ± 6.7 (fixed-dosing) letters (least squares mean difference [95% confidence interval]: T&E 0.01 [− 1.46, 1.47] and PRN 0.95 (− 0.52, 2.42) letters versus fixed dosing; $p < 0.0001$ for both non-inferiority tests [4-letter margin]). The IVT-AFL safety profile was consistent with previous studies.
Conclusion: The treatment burden associated with intravitreal injections for DME is lowest with T&E regimens, but there are a range of flexible IVT-AFL dosing regimens, allowing physicians to adopt an individualized treatment plan.
Trial Registration: ClinicalTrials.gov identifier: NCT02818998.**Keywords:** Aflibercept; Diabetic retinopathy; Intravitreal injections; Macular edema; Treatment outcome; Vascular endothelial growth factor

Key Summary Points

Why carry out this study?

There is a lack of data regarding the best regimen to optimize functional and anatomical outcomes with long-term intravitreal aflibercept (IVT-AFL) treatment in patients with diabetic macular edema

What did the study ask? / What was the hypothesis of the study?

In the phase 3b, randomized, non-inferiority VIOLET study, we investigated whether flexible IVT-AFL dosing (treat and-extend [T&E] or pro re nata [PRN]) was comparable to fixed dosing every 8 weeks (q8w), beyond the first year of treatment in patients with DME

What was learned from the study?

In patients who previously received ≥ 1 year of IVT-AFL for DME, both flexible IVT-AFL treatment regimens (T&E and PRN) achieved similar functional outcomes to fixed dosing (IVT-AFL q8w) at Week 52 (primary endpoint) and Week 100. The safety profile was consistent with that known for IVT AFL

A range of IVT-AFL dosing regimens allow selection of individualized treatment plans

INTRODUCTION

Diabetic macular edema (DME) is a manifestation of diabetic retinopathy and the leading cause of visual impairment in people with diabetes [1]. DME prevalence is predicted to increase over time due to rising rates of diabetes, an aging population and the increased life expectancy of those with diabetes [2]. First-line treatment for the management of DME is anti-vascular endothelial growth factor (anti-VEGF)

agents, such as intravitreal aflibercept (IVT-AFL) and ranibizumab [3].

The VIVID-DME (Intravitreal Aflibercept Injection in Vision Impairment Due to DME) and VISTA-DME (Study of Intravitreal Aflibercept Injection in Patients With Diabetic Macular Edema) Phase III studies showed that treatment with IVT-AFL fixed dosing every 4 or 8 weeks, following five initial monthly doses, was associated with significant improvements in functional outcomes compared with laser treatment, and outcomes were maintained over 3 years in patients with DME [4–6]. As an alternative to fixed dosing, two flexible treatment strategies are available for the administration of IVT-AFL: treat-and-extend (T&E) and as-needed pro re nata (PRN) regimens [7]. The aim of flexible management of patients with DME is to reduce the treatment burden associated with anti-VEGF therapy, while maintaining visual acuity gains [8]. T&E involves gradual extension of the treatment interval based on maintenance of functional and anatomical stability, and shortening of the treatment interval if deterioration is observed. This approach reduces the frequency of clinic visits and removes the requirement for monitoring between injections, making the disease more manageable for the patient and physician. PRN involves treatment on an as-needed basis, with regular monthly visits being required for monitoring [8].

Availability of a choice of dosing regimens means that the physician and patient can select the treatment option that best suits individual needs and addresses the burden of treatment. However, there is a lack of data regarding the best regimen to optimize functional and anatomical outcomes with long-term IVT-AFL treatment in patients with DME. The aim of the VIOLET study was to assess whether IVT-AFL administered according to two different flexible dosing regimens provided similar efficacy and safety to fixed dosing every 8 weeks (q8w) in patients with DME who had already completed 1 year of IVT-AFL treatment. Here, we report the 52- and 100-week outcomes from the VIOLET study.

METHODS

VIOLET was a 100-week, multicenter, randomized, open-label, active-controlled, parallel-group, Phase IIIb, non-inferiority study that investigated whether IVT-AFL administered according to two different flexible-dosing regimens (T&E and PRN) provided similar efficacy and safety to fixed-dosing q8w in patients with DME who had already completed ≥ 1 year of IVT-AFL treatment.

The study was conducted at 64 sites in Europe and Canada from November 2016 to September 2019 and in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines E6: Good Clinical Practice. The study protocol and statistical analysis plan can be accessed at ClinicalTrials.gov (identifier: NCT02818998). The protocol was approved by the independent ethics committee or institutional review board at each study site (see Supplementary Material for full details). All patients provided written informed consent.

Study Design

Patients enrolled in the VIOLET study had received treatment with IVT-AFL 2 mg for at least 1 year, initiated with five monthly injections, followed by treatment q8w until enrollment (one missed or delayed q8w dose was permissible) (Fig. S1). Patients were enrolled from either the AQUA study (NCT02581995; an open-label, single-arm study designed to evaluate vision-related quality of life in patients who received five initial monthly injections of IVT-AFL 2 mg, followed by treatment q8w until Week 52) or from outside the AQUA study, if they fulfilled the eligibility criteria. Details of the AQUA study are published elsewhere [9].

In the VIOLET study, if all data needed for enrollment were available, the screening and baseline visits could take place on the same day. In such cases, procedures scheduled for both visits were conducted only once. Randomization (1:1:1) was conducted at Week 0 (baseline) and was stratified according to whether patients had achieved a ≥ 10-letter gain in best-

Table 1 Administration schedule and re-treatment criteria

IVT-AFL fixed	
Fixed treatment intervals q8w throughout the entire treatment period	**Treatment cessation**
After the baseline visit, patients returned q8w to the investigational site	Usually, treatment should not be ceased in this reference arm. However, temporary treatment cessation could have been considered if the investigator had reason to believe that, at the respective time point, treatment was not in the patient's best interest
An injection was administered every visit from baseline to Week 96	The patient was to return for evaluation as the investigator considered appropriate, depending on the patient's condition
The final safety and efficacy assessments were conducted at Week 100	**Treatment re-start**
There were no monitoring visits without treatment (except for Weeks 52 and 100)	Treatment was to be re-started once the condition leading to cessation of treatment had resolved
	In case of recurrence of DME, it was proposed to begin with the same regimen as a de novo treatment, i.e. five monthly injections followed by treatment q8w
IVT-AFL T&E	
Flexible treatment intervals: ≥ 8 weeks (no upper limit)	**Treatment cessation**
At the baseline visit and at each subsequent visit, the investigator determined the duration until the patient's next injection, based on visual and anatomical outcomes at the current visit	Cessation of treatment could be considered if the interval between two injections reached or exceeded 16 weeks and if this duration could be maintained for ≥ 2 consecutive intervals without the need for shortening of the interval, i.e. with stable visual and anatomical outcome parameters
Treatment intervals could have been extended if visual and anatomical measures were stable	If treatment was halted, the patient had to return for monitoring visits at least every 16 weeks
When/if edema recurred, the treatment interval was reverted to the last treatment interval when the disease was inactive. The increments and decrements for the treatment intervals were at the investigator's discretion; typically, increments of 2 weeks were recommended	**Treatment re-start**
	Treatment was to be re-started if a deterioration of visual and anatomical outcome parameters occurred
An injection was given at each visit, with the (potential) exception of Weeks 52 and 100. At Weeks 52 and 100, an injection could have been given if this visit coincided with a scheduled injection visit	If treatment was re-started due to recurrence of DME, it was proposed to begin with the same regimen as a de novo treatment, i.e. five monthly injections followed by treatment q8w
All patients returned for efficacy and safety assessments at Weeks 52 and 100[a]	
IVT-AFL PRN	
After randomization, the patients had a visit every 4 weeks. At each visit, the investigator determined, based on pre-specified re-treatment criteria, whether an injection was to be given or not:	**Treatment cessation**
Leakage as a sign of active DME (e.g. CRT as assessed by SD-OCT > 300 µm and/or an increase of > 50 µm from best previous measurement)	If there was no recurrence of active disease, treatment was terminated until such time, if ever, that the disease recurred. The monthly monitoring was to continue throughout
Increase of ≥ 5 letters in BCVA between current and most recent previous visit	**Treatment re-start**
Loss of ≥ 5 letters from the best previous BCVA measurement with any increase in SD-OCT CRT	Treatment was to be resumed with single injections each time the re-treatment criteria were met
The last visit with an option for treatment under the protocol was at Week 96	
Final safety and efficacy assessments were done at Week 100	

AE adverse event, *BCVA* best-corrected visual acuity, *CRT* central retinal thickness, *DME* diabetic macular edema, *IVT-AFL* intravitreal aflibercept, *PRN* pro re nata, *q8w* every 8 weeks, *SD-OCT* spectral domain optical coherence tomography, *T&E* treat-and-extend

[a]If an extended-dosing patient received an injection at Week 100, it was the responsibility of the treating investigator to follow up on any AEs (including ongoing events) that occurred within 4 weeks following this treatment. Information regarding such events was reported under the protocol (i.e. not as spontaneous reports)

corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS]) from the start of IVT-AFL treatment (≥ 1 year before baseline).

Patients were randomly assigned to treatment with IVT-AFL according to a fixed-dose, PRN, or T&E regimen, as detailed in Table 1. Further details of the methods are available in the Supplementary Material.

Patients

Patients who had received prior treatment with IVT-AFL for ≥ 1 year under the guidance of the European label – five initial monthly IVT-AFL 2 mg injections, followed by an IVT-AFL injection q8w (for patients enrolled from the AQUA study [9]) or treatment within allowed time windows for interval deviations (patients enrolled outside the AQUA study) – were eligible for inclusion. Patients were aged ≥ 18 years, with type 1 or type 2 diabetes mellitus and DME with central macular involvement (defined as the area of the center subfield on spectral domain optical coherence tomography [OCT]), BCVA 73–24 ETDRS letters (20/40–20/320 Snellen equivalent) in the study eye at pre-study treatment initiation. Only one eye was designated as the study eye. See Supplementary Material for full details.

Endpoints

The primary endpoint was assessed at Week 52, the end of the first year of treatment under the protocol. Thus, patients who completed 1 year in the study had completed 2 years of treatment with IVT-AFL in total. The primary endpoint was the mean change in BCVA (ETDRS letters) from baseline to Week 52 with IVT-AFL 2 mg (after 2 years of treatment). Secondary endpoints were the mean change in BCVA from baseline to Week 100, mean change in central retinal thickness (CRT) from baseline to Weeks 52 and 100, and the proportion of patients with BCVA gains of ≥ 10 or ≥ 15 ETDRS letters (two or three Snellen lines, respectively) and losses of ≥ 30 ETDRS letters (six Snellen lines) from baseline to Weeks 52 and 100. See Supplementary Material for other endpoints.

Statistical Analysis

A sample size of 135 evaluable patients per treatment group was planned. Assuming an equal mean change in BCVA from baseline to Week 52 in the treatment groups, a standard deviation (SD) of 9, 11, and 11 ETDRS letters for the mean BCVA change from baseline to Week 52 in the fixed, T&E, and PRN groups, respectively, and a family-wise error rate alpha of 2.5% (one-sided tests), this sample size provided power of 90% to demonstrate non-inferiority at a non-inferiority margin of 4 letters for either T&E versus fixed regimens, or for the comparison of the PRN versus fixed regimens at a significance level of 2.5% (one-sided test). The expected dropout rate was estimated to be 17% [5]; thus, approximately 490 patients were planned to be randomized (the final number of patients was lower; see Supplementary Material for details). The primary analysis was based on an analysis of covariance (ANCOVA) model with the baseline BCVA measurement as covariate and the treatment regimen and stratum (10-letter gain from start of IVT-AFL treatment [yes/no]) as fixed factors. The Hochberg procedure was used to control the overall type-1 error of 2.5% (one-sided tests) for the two non-inferiority tests. The full analysis set (FAS) included all randomized patients who received the study drug and had a baseline BCVA assessment and at least one post-baseline BCVA assessment; the primary statistical analysis was performed on the FAS. The primary method for replacing missing values for all efficacy analyses was last observation carried forward. Secondary endpoints were analyzed descriptively, including 95% confidence intervals (CIs) where appropriate. Statistical evaluation was performed using Statistical Analysis Software v9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

In total, 500 patients were enrolled and 463 were randomly assigned to treatment. The FAS

was comprised of 458 patients (n = 153 [fixed], n = 152 [T&E], and n = 153 [PRN]). Two patients in each of the fixed and T&E groups and one patient in the PRN group had no post-baseline assessments available and were excluded from the FAS. More than 95% of patients enrolled after completing the AQUA study, in which > 90% of patients received all nine IVT-AFL injections in Year 1 per the protocol (mean number of injections: 8.8 [95% CI 8.7–8.9]) [9]. The Week 100 visit was completed by 88.4% (n = 137), 89.6% (n = 138), and 88.3% (n = 136) of patients in the fixed, T&E, and PRN groups, respectively (Fig. 1).

Patient baseline demographics and disease characteristics were similar between the groups (Table 2). Mean age was 64.4–65.5 years across the groups and 58.2–64.1% of patients were male. Mean BCVA was 72.7, 72.5, and 71.0 letters (approximately 20/32 to 20/40 Snellen equivalent) in the fixed, T&E, and PRN groups, respectively, and mean CRT was 289.9 μm, 285.9 μm, and 294.6 μm, respectively.

Over 52 weeks, patients received a mean (min–max) of 6.7 (1–7; fixed), 5.6 (1–7; T&E), and 6.2 (1–13; PRN) injections. Over 100 weeks, patients received a mean (min–max) of 12.3 (3–13; fixed), 10.0 (2–14; T&E), and 11.5 (1–25; PRN) injections (Figs. S2A and S2B), which occurred during a mean 95.5, 94.8, and 84.9 weeks of exposure to IVT-AFL, respectively. The mean (min–max) number of clinic visits, including Weeks 52 and 100, was 16.1 (5–25; fixed), 13.3 (4–23; T&E), and 25.0 (3–29; PRN). The mean (range) number of visits per patient-year was 8.8 (7–16; fixed), 7.2 (5–12; T&E), and 14.2 (10–31; PRN). The mean (SD) last treatment interval was 8.0 (0.7), 11.5 (4.9), and 11.8 (14.3) weeks for the fixed, T&E, and PRN groups, respectively. Overall, in accordance with the protocol, no patients in the fixed group achieved a last treatment interval up to Week 100 of ≥ 12 weeks; 40.8% (n = 62) and 32.0% (n = 49) of patients in the T&E and PRN groups achieved a last treatment interval of ≥ 12 weeks.

At Week 52, mean (SD) BCVA change from baseline was + 0.4 (6.7; fixed), + 0.5 (6.7; T&E), and + 1.7 (6.8; PRN) (Fig. 2). Least squares mean difference (95% CI) to IVT-AFL fixed dosing was 0.01 (− 1.46, 1.47) letters for the T&E regimen and 0.95 (− 0.52, 2.42) letters for

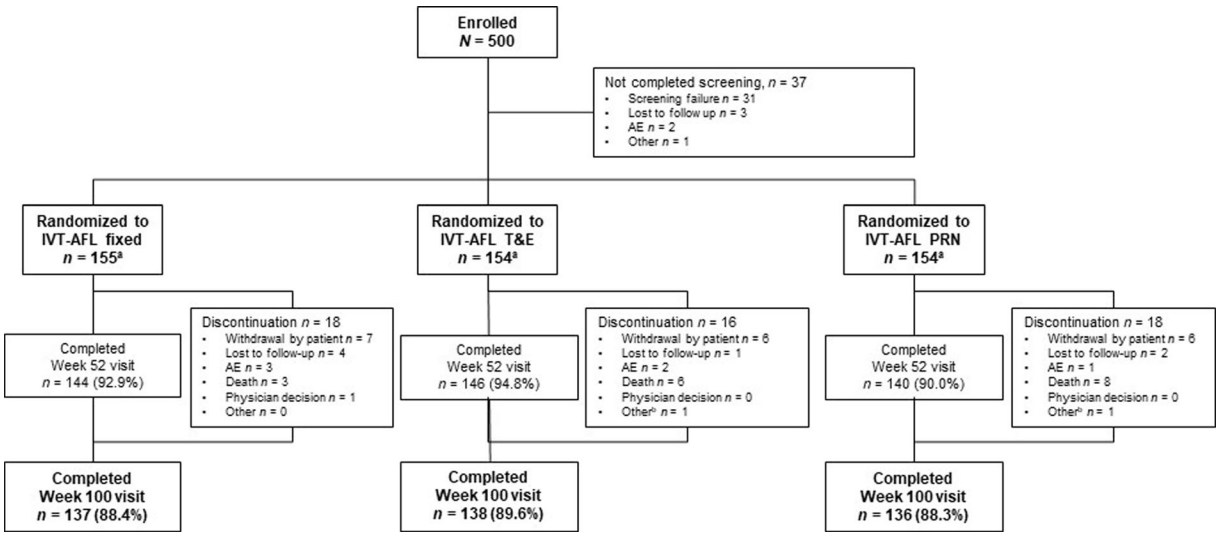


Fig. 1 Patient disposition. [a]Two patients in each of the fixed and T&E groups and one patient in the PRN group had no post-baseline assessments available and were excluded from the full analysis set. [b]Reasons for withdrawal in the category "Other" were patient withdrawal by sponsor and lack of efficacy. *AE* adverse event, *IVT-AFL* intravitreal aflibercept, *PRN* pro re nata, *T&E* treat-and-extend

Table 2 Patient baseline demographics and disease characteristics (FAS)

Characteristic	IVT-AFL fixed (*N* = 153)	IVT-AFL T&E (*N* = 152)	IVT-AFL PRN (*N* = 153)
Mean age, years (SD)	64.4 (8.6)	64.7 (10.1)	65.5 (9.2)
Age range, years			
18–64	71 (46.4)	69 (45.4)	67 (43.8)
65–84	82 (53.6)	83 (54.6)	84 (54.9)
≥ 85	0	0	2 (1.3)
Sex			
Male	98 (64.1)	94 (61.8)	89 (58.2)
Race			
White	139 (90.8)	142 (93.4)	146 (95.4)
Black	1 (0.7)	0	0
Asian	2 (1.3)	1 (0.7)	0
Not reported	11 (7.2)	9 (5.9)	7 (4.6)
HbA_{1c}			
Mean (SD)	7.7 (1.4)	7.7 (1.3)	7.8 (1.3)
> 8%	55 (35.9)	52 (34.2)	51 (33.3)
≤ 8%	93 (60.8)	96 (63.2)	100 (65.4)
Prior participation in the AQUA study			
Yes	145 (94.8)	144 (94.7)	148 (96.7)
No	8 (5.2)	8 (5.3)	5 (3.3)
Mean BVCA ETDRS letters (SD)			
At start of IVT-AFL treatment	62.2 (10.7)	62.6 (10.8)	60.5 (11.4)
At VIOLET study baseline	72.7 (10.4)	72.5 (11.4)	71.0 (10.9)
Change from start of IVT-AFL treatment to VIOLET study baseline	10.5 (7.6)	10.0 (7.3)	10.4 (9.7)
Mean CRT, μm (SD)	289.9 (66.8)	285.9 (76.3)	294.6 (81.0)
DRSS[a]			
DR absent (10)	2 (1.3)	0	0
DR questionable (15)	0	1 (0.7)	0
Microaneurysms only (20)	1 (0.7)	2 (1.3)	0
Mild NPDR (35)	84 (54.9)	94 (61.8)	89 (58.2)
Moderate NPDR (43)	47 (30.7)	36 (23.7)	44 (28.8)
Moderately severe NPDR (47)	9 (5.9)	10 (6.6)	13 (8.5)

Table 2 continued

Characteristic	IVT-AFL fixed (*N* = 153)	IVT-AFL T&E (*N* = 152)	IVT-AFL PRN (*N* = 153)
Severe NPDR (53)	0	4 (2.6)	4 (2.6)
Mild PDR (61)	6 (3.9)	2 (1.3)	0
High-risk PDR (71)	0	0	1 (0.7)
Cannot grade (90)	4 (2.6)	3 (2.0)	2 (1.3)

Values are *n* (%) unless otherwise stated. Patients had previously received 1 year of IVT-AFL treatment prior to the VIOLET study baseline; data are for VIOLET study baseline unless otherwise stated

BVCA best-corrected visual acuity, *CRT* central retinal thickness, *DR* diabetic retinopathy, *DRSS* Diabetic Retinopathy Severity Score, *ETDRS* Early Treatment Diabetic Retinopathy Study, *FAS* full analysis set, HbA_{1c} glycated hemoglobin, *IVT-AFL* intravitreal aflibercept, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *PRN* pro re nata, *SD* standard deviation, *T&E* treat-and-extend

[a]Based on 7-field fundus photography images

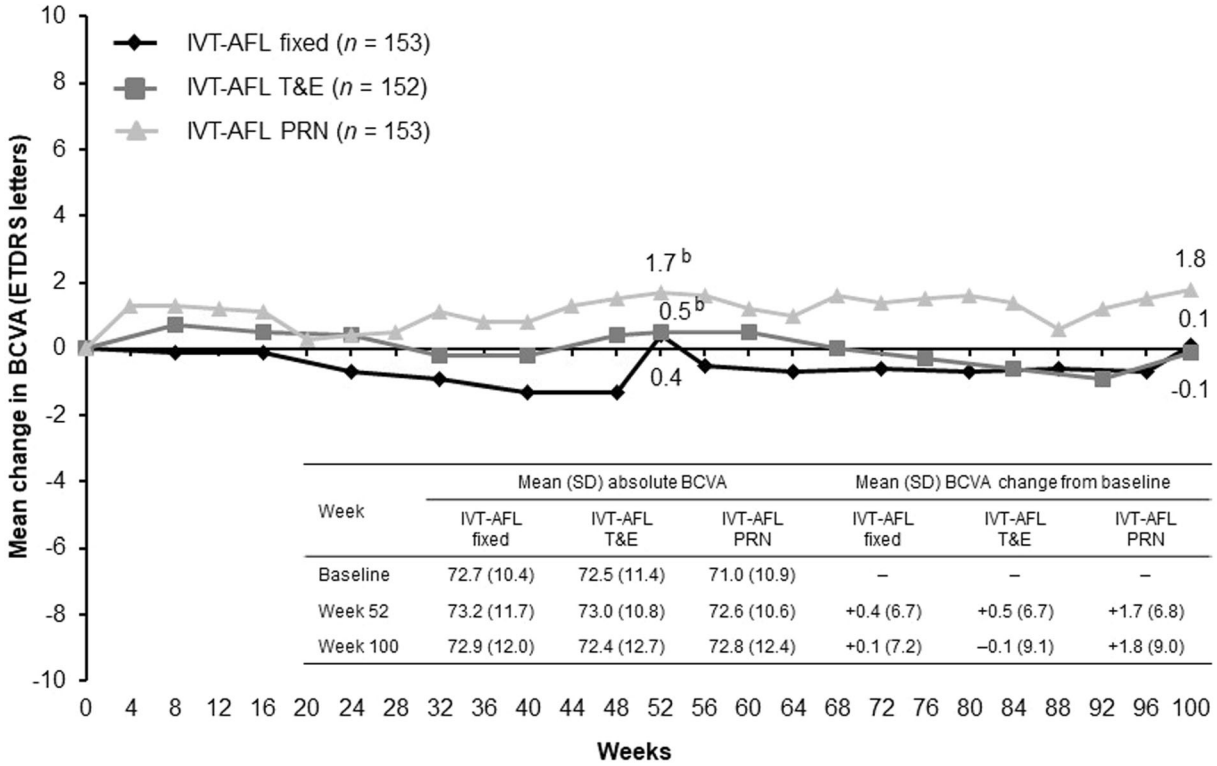
the PRN regimen. Compared with fixed dosing, both flexible regimens achieved a non-inferior outcome in mean BCVA change for the pre-specified margin of 4 letters ($p < 0.0001$ for both comparisons).

Mean (SD) BCVA change from baseline was + 0.1 (7.2; fixed), − 0.1 (9.1; T&E), and + 1.8 (9.0; PRN) at Week 104 (Fig. 2). Least squares mean difference (95% CI) to IVT-AFL fixed dosing was − 0.30 (− 2.13, 1.52) letters for the T&E regimen and 1.39 (− 0.40, 3.19) letters for the PRN regimen. Findings at Week 100 confirmed results from Week 52 and achieved nominal significance for non-inferiority ($p < 0.0001$). Absolute BCVA values at baseline, Week 52, and Week 100 are shown in Fig. 2. The within-group changes observed over the 100-week study period were similar across groups. Mean change in BCVA from the start of the previous IVT-AFL treatment to Week 100 of the VIOLET study is presented in Fig. S3. Both Fig. 2 and Fig. S3 present data according to a last observation carried forward approach. A supporting observed cases analysis (data not shown) indicated that the results and their interpretation were not affected by missing data.

At Week 52, gains of ≥ 10 and ≥ 15 letters (two to three Snellen lines) respectively, were observed in 6.5% and 2.6% (fixed), 9.2% and 3.3% (T&E), and 8.5% and 2.6% (PRN) of patients (Fig. S4). A loss of ≥ 30 letters (or six Snellen lines) was observed in one patient (0.7%) in the fixed group, and no patients in either of the T&E or PRN groups. At Week 100, gains of ≥ 10 and ≥ 15 letters, respectively, were observed in 6.5% and 2.0% (fixed), 11.2% and 2.6% (T&E), and 14.4% and 3.9% (PRN) of patients. A loss of ≥ 30 letters was observed in 1/153 (0.7%), 2/152 (1.3%), and 2/153 (1.3%) of patients in the fixed, T&E, and PRN groups, respectively.

Except for baseline, Week 52, and Week 100, CRT measurements were only mandatory for patients in the PRN arm and were conducted in the fixed-dose and T&E arms when clinically indicated per investigator judgment. Mean (SD) CRT change (μm) from baseline was − 18.8 (45.5; fixed), − 2.1 (56.2; T&E), and + 2.2 (77.8; PRN) at Week 52. Least squares mean difference (95% CI) to IVT-AFL fixed dosing was 14.38 (3.39, 25.37) μm for the T&E regimen and 21.22 (7.65, 34.80) μm for the PRN regimen. At Week 100, mean (SD) CRT change (μm) from baseline was − 15.5 (64.3; fixed), + 2.3 (81.8; T&E), and − 13.9 (74.4; PRN). Least squares mean difference (95% CI) to IVT-AFL fixed dosing was 16.14 (0.62, 31.66) μm for the T&E regimen and 4.12 (− 9.52, 17.77) μm for the PRN regimen.

At Week 52 (in the second year of treatment), 4.4% (fixed), 5.0% (T&E), and 3.8% (PRN) of patients achieved a ≥ 2-step



Week	Mean (SD) absolute BCVA			Mean (SD) BCVA change from baseline		
	IVT-AFL fixed	IVT-AFL T&E	IVT-AFL PRN	IVT-AFL fixed	IVT-AFL T&E	IVT-AFL PRN
Baseline	72.7 (10.4)	72.5 (11.4)	71.0 (10.9)	–	–	–
Week 52	73.2 (11.7)	73.0 (10.8)	72.6 (10.6)	+0.4 (6.7)	+0.5 (6.7)	+1.7 (6.8)
Week 100	72.9 (12.0)	72.4 (12.7)	72.8 (12.4)	+0.1 (7.2)	–0.1 (9.1)	+1.8 (9.0)

Fig. 2 Mean change in BCVA from baseline to Week 100[a]. Full analysis set; last observation carried forward. The apparent spike at Week 52 and Week 100 is because this was a mandatory visit for all patients. [a]Patients had previously received 1 year of IVT-AFL treatment prior to the VIOLET study baseline. [b]At Week 52 (primary endpoint), compared with IVT-AFL fixed, IVT-AFL T&E, and IVT-AFL PRN groups achieved a non-inferior outcome in mean BCVA change for the prespecified margin of 4 letters ($p < 0.0001$ for both comparisons). *BCVA* best-corrected visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IVT-AFL* intravitreal aflibercept, *PRN* pro re nata; *SD* standard deviation, *T&E* treat-and-extend

improvement in the Diabetic Retinopathy Severity Score (DRSS) and 2.2% (*n/N* = 3/135) of patients in the fixed group achieved a ≥ 3-step improvement in DRSS. No patients in the T&E and PRN groups achieved a ≥ 3-step improvement in DRSS at Week 52. At Week 100 (in the third year of treatment), overall, 4.9% of patients experienced either a two-step improvement or a two-step worsening in DRSS during the study (Table 3).

The incidence of ocular treatment-emergent adverse events was comparable in the fixed (52.9%), T&E (52.6%), and PRN (55.2%) groups. The safety profile was consistent with results from prior studies of IVT-AFL [4–6] and only 2 patients experienced intraocular inflammation events, which were mild and transient in nature (Table 4). The overall incidence of arterial thromboembolic events defined by the Anti-Platelet Trialists' Collaboration criteria was 3.2% (fixed), 1.9% (T&E), and 3.9% (PRN) of patients. Overall, 17 deaths were reported: three (1.9%) fixed, six (3.9%) T&E, and eight (5.2%) PRN (Table S1). The incidence of treatment-emergent deaths in the fixed, T&E, and PRN groups was one (0.6%), three (1.9%), and four (2.6%), respectively (Table S2).

DISCUSSION

The VIOLET study showed that, in patients who had already received at least 1 year of IVT-AFL treatment for DME under the guidance of the European label, both flexible IVT-AFL treatment regimens (T&E and PRN) achieved a non-

Table 3 Patients with a ≥ 2-step and ≥ 3-step improvement or worsening at Weeks 52 and 100 from baseline

	IVT-AFL fixed *n/N* (%)	IVT-AFL T&E *n/N* (%)	IVT-AFL PRN *n/N* (%)
Week 52			
≥ 2-step improvement	6/135 (4.4)	7/141 (5.0)	5/132 (3.8)
≥ 3-step improvement	3/135 (2.2)	0/141 (0.0)	0/132 (0.0)
≥ 2-step worsening	8/128 (6.3)	4/131 (3.1)	7/127 (5.5)
≥ 3-step worsening	3/128 (2.3)	1/131 (0.8)	4/127 (3.1)
Week 100[a]			
≥ 2-step improvement	9/128 (7.0)	7/131 (5.3)	3/127 (2.4)
≥ 3-step improvement	4/128 (3.1)	3/131 (2.3)	0/127 (0.0)
≥ 2-step worsening	8/128 (6.3)	4/131 (3.1)	7/127 (5.5)
≥ 3-step worsening	3/128 (2.3)	1/131 (0.8)	4/127 (3.1)

Observed cases. Patients had previously received 1 year of IVT-AFL treatment prior to the VIOLET study baseline
IVT-AFL intravitreal aflibercept, *PRN* pro re nata, *T&E* treat-and-extend
[a]*N* = 386

inferior outcome in mean BCVA change compared with fixed dosing (IVT-AFL 2 mg q8w) at Week 52 (primary endpoint) and Week 100. No clinically relevant differences were observed between the IVT-AFL fixed and T&E groups, or between the fixed and PRN groups, for the changes in BCVA letter score at Week 52 and Week 100. Differences in CRT changes between treatment groups were not clinically meaningful. Of the three regimens investigated, a reduced treatment burden was observed in the T&E group, which received the lowest number of injections. Furthermore, T&E dosing was associated with a reduced mean number of clinic visits.

Most patients in the VIOLET study had participated in the AQUA study and, in that study, achieved a mean gain in BCVA of + 10 letters after 1 year of treatment [9]; therefore, no substantial improvements were expected during the VIOLET study. Improvements in BCVA and CRT achieved in the year prior to enrollment in VIOLET were maintained over the second and third years of treatment with either a fixed, T&E, or PRN dosing regimen. Furthermore, late visual gain was observed in 2–3% of patients who gained ≥ 15 letters in the second and third years of treatment in this study. Thus, unlike neovascular age-related macular degeneration (nAMD), where treatment delays of as little as 6 weeks impact functional outcome [10, 11], the exact timing of treatment is less critical in DME. Indeed, functionally driven treatment is likely to work well, and this helps to explain why, in contrast to nAMD, PRN and T&E work similarly well regarding functional outcomes. In this study, in addition to a mean 10-letter gain with IVT-AFL treatment prior to randomization, more than 20% of patients with DME gained ≥ 5 letters in the second year of treatment with IVT-AFL. Most longer-term studies of anti-VEGF agents report change from baseline rather than change beyond Year 1; however, fluid persisting over 2 years is not a rare or atypical finding [12]. Even if a complete response to treatment is not achieved in the first year, treatment continuation will not only prevent further visual deterioration, but may result in a valuable late functional gain in a relevant proportion of patients. Identification of baseline factors associated with outcomes in DME may help to inform physicians regarding treatment

Table 4 Safety overview at Week 100

Number of patients (%)	**IVT-AFL fixed (*N* = 155)**	**IVT-AFL T&E (*N* = 154)**	**IVT-AFL PRN (*N* = 154)**
Any AE	134 (86.5)	131 (85.1)	140 (90.9)
Any ocular AE	106 (68.4)	110 (71.4)	115 (74.7)
Any TEAE	129 (83.2)	128 (83.1)	129 (83.8)
Any ocular TEAE	100 (64.5)	105 (68.2)	104 (67.5)
Any ocular TEAE in the study eye	82 (52.9)	81 (52.6)	85 (55.2)
Any non-ocular TEAE	102 (65.8)	85 (55.2)	101 (65.6)
Any TEAE causally related to IVT-AFL	1 (0.6)	0	2 (1.3)
Maximum intensity for any TEAE			
Mild	43 (27.7)	55 (35.7)	46 (29.9)
Moderate	59 (38.1)	54 (35.1)	60 (39.0)
Severe	27 (17.4)	19 (12.3)	23 (14.9)
Ocular TEAEs in the study eye $\geq$ 5%			
Cataract	25 (16.1)	24 (15.6)	18 (11.7)
Reduced visual acuity	18 (11.6)	17 (11.0)	14 (9.1)
Increased intraocular pressure	11 (7.1)	3 (1.9)	9 (5.8)
Macular edema	1 (0.6)	7 (4.5)	10 (6.5)
Maculopathy[a]	2 (1.3)	1 (0.6)	10 (6.5)
Cystoid macular edema	8 (5.2)	1 (0.6)	5 (3.2)
Cataract nuclear	8 (5.2)	0	5 (3.2)
Diabetic retinopathy	7 (4.5)	7 (4.5)	8 (5.2)
Posterior capsule opacification	3 (1.9)	5 (3.2)	8 (5.2)
Any SAE	42 (27.1)	46 (29.9)	42 (27.3)
Any treatment-emergent SAE	35 (22.6)	38 (24.7)	37 (24.0)
Any treatment-emergent SAE causally related to IVT-AFL	0	0	0
Discontinuation of study drug due to AEs	3 (1.9)	2 (1.3)	2 (1.3)
Discontinuation of study drug due to TEAEs	1 (0.6)	0	0
Any APTC event	5 (3.2)	3 (1.9)	6 (3.9)
Any deaths	3 (1.9)	6 (3.9)	8 (5.2)
Any treatment-emergent deaths	1 (0.6)	3 (1.9)	4 (2.6)

Table 4 continued

Number of patients (%)	IVT-AFL fixed (*N* = 155)	IVT-AFL T&E (*N* = 154)	IVT-AFL PRN (*N* = 154)
Intraocular inflammation[b]	0	1 (0.7)	1 (0.7)

Safety analysis set. Patients with DME who had already completed 1 year of IVT-AFL treatment

AE adverse event, *APTC* Anti-Platelet Trialists' Collaboration, *DME* diabetic macular edema, *IVT-AFL* intravitreal aflibercept, *PRN* pro re nata, *SAE* serious adverse event, *T&E* treat-and-extend, *TEAE* treatment-emergent adverse event

[a]Increase in central retinal thickness

[b]Mild and transient in nature

expectations and support identification of patients who may be late responders. This has previously been investigated at 12 months in patients treated with intravitreal ranibizumab [13], and requires further research in patients treated with IVT-AFL.

Although little is known regarding the dynamics of DRSS changes due to anti-VEGF therapy in the long term, most of the improvement in DRSS was achieved prior to the study during the first 12 months of treatment (during which 20.5% and 3.4% of patients had a $\geq$ 2- and $\geq$ 3-step DRSS improvement, respectively [9]), which is consistent with previous findings [4]. The present study provides evidence that proportions of change in DRSS remain stable for a further 2 years following the first year of treatment with IVT-AFL.

As patients with DME are usually younger than those with nAMD [14], long-term treatment is often required. Thus, the availability of easy-to-manage and flexible treatment strategies that meet individual patient needs are important. The Diabetic Retinopathy Clinical Research Network (DRCR.net) has contributed to substantial advances in the relative benefits of anti-VEGF agents as the first-line therapy for eyes with visual impairment due to DME. Protocol I, the first study of an anti-VEGF agent, ranibizumab PRN (compared with non-anti-VEGF treatment), demonstrated 8–9 letter gains after 1 year of treatment, with improvements being maintained up to 5 years [15, 16]. It became apparent that fewer injections were needed after the first year of treatment, and the majority of patients did not receive anti-VEGF injections during the fifth year of treatment [16]. Protocol T, which compared ranibizumab 0.3 mg with IVT-AFL and bevacizumab (using the same regimen, with a modified PRN protocol based on vision and OCT findings), demonstrated that IVT-AFL was more effective at improving vision in patients with worse levels of visual acuity ($\leq$ 65 letters) after 1 and 2 years of treatment [17, 18]. Beyond Year 2 to the end of Year 5, two-thirds of study eyes received at least one anti-VEGF injection (median four injections in 3 years; interquartile range 0–12); visual acuity was improved from baseline after 5 years of treatment, driven by gains in Year 1 and 2, as visual acuity decreased in Years 3–5 compared with the end of Year 2 [19]. Both Protocol T and Protocol I assessed the role of deferred laser photocoagulation within the management of patients with DME, but neither were designed to compare different anti-VEGF treatment regimens. Thus, VIOLET adds to this evidence base by evaluating three different treatment regimens with a single anti-VEGF agent.

The VIOLET study explored the use of flexible-dosing IVT-AFL regimens, allowing physicians to adopt the optimal treatment plan based on individual patient needs and clinical practice requirements [7, 8]. The PRN regimen included monthly visits, which may have an impact on adherence in real-world clinical practice due to the frequency of visits and increased burden for patients and physicians due to clinic constraints. Under T&E, treatment intensity is adapted to individual needs, which is more readily accepted and more likely to be adhered

to by patients. Treatment is administered at every visit under a T&E protocol, which helps to plan clinic capacity. Furthermore, as the patient knows that they will be treated at every visit, they are prepared to receive an injection, and any uncertainty about treatment is eliminated [8]. In this clinical trial setting, the number of injections and subsequent functional outcomes were similar with PRN and T&E dosing. However, the burden of treatment in terms of clinic visits differed, with a notably higher number of visits in the PRN group (25.0 compared with 16.1 [fixed] and 13.3 [T&E] visits). This was due to the nature of the PRN regimen, whereby patients were required to attend the clinic monthly, but did not receive an injection at every visit. Given the flexible nature of the proactive, individualized T&E regimen, 40.8% of patients achieved a treatment interval of $\geq$ 12 weeks, compared with 32.0% of patients receiving PRN IVT-AFL (and no patients receiving fixed dosing). In real-world clinical practice, it is likely that reduced clinic visits may have a positive impact on treatment adherence [8].

Regarding study strengths, we investigated the direct comparison of three IVT-AFL regimens, including T&E dosing, from the second year of treatment when physicians are often facing decisions regarding choice of management strategy. Furthermore, this was a long-term study with a large sample size. The safety profile of IVT-AFL for the treatment of DME in this study was consistent with results from prior studies [4–6]. Limitations include that the results refer to a largely White population and that two-thirds of patients had a glycated hemoglobin value below 8% at baseline, indicating a potential selection bias toward diabetes treatment-compliant patients. In addition, at baseline, most patients had mild-to-moderate diabetic retinopathy, thus limiting the interpretation of DRSS responses.

CONCLUSIONS

Results from the VIOLET study demonstrate that, in patients who received at least 1 year of IVT-AFL treatment for DME under the guidance of the European label, both flexible IVT-AFL treatment regimens (T&E and PRN) resulted in similar functional outcomes to fixed dosing (IVT-AFL 2 mg q8w) in the second and third years of treatment, with the T&E group requiring the lowest number of injections and clinic visits. Findings highlight the range of flexible-dosing regimens available with IVT-AFL, allowing physicians to adopt the optimal treatment plan based on individual patient needs and clinical practice requirements.

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Data Availability. Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded. The study protocol and statistical analysis plan can be accessed at ClinicalTrials.gov (Identifier: NCT02818998).

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