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ORIGINAL RESEARCH

XTEND: Two-Year Results from a Global Observational Study Investigating Proactive Dosing of Intravitreal Aflibercept in Neovascular Age-Related Macular Degeneration

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ABSTRACT

Introduction: XTEND (NCT03939767) is a multicenter, observational, prospective study of patients with treatment-naïve neovascular age-related macular degeneration (nAMD) in routine clinical practice. The study aims to examine treatment outcomes of proactive intravitreal aflibercept (IVT-AFL) treatment regimens (fixed dosing or treat-and-extend) according to local marketing labels.

Methods: Study eyes received IVT-AFL injections as per the local label. The mean changes in best-corrected visual acuity (BCVA) and central subfield thickness (CST) from baseline to month (M) 12 and M24 were measured and stratified by baseline factors. Treatment exposure and safety data were evaluated. Statistical analysis was descriptive.

Results: Overall, 1466 patients from 17 countries were treated. For the overall population, the mean ± standard deviation (SD) age was 78.7 ± 8.5 (range 50–100) years, and 891 patients (60.8%) were female. The mean ± SD baseline BCVA was 54.3 ± 20.3 letters and CST was 374 ± 126 µm. At M12 and M24, mean (95% confidence interval [CI]) BCVA change was + 4.3 (3.4, 5.3) and + 2.3 (1.3, 3.3) letters, respectively.

Prior presentation: Data in this manuscript were published as an oral presentation at the Association for Research in Vision and Ophthalmology (ARVO) 2023 Annual Meeting (23–27 April 2023; New Orleans, LA, USA). One-year data from the XTEND study were presented at the 2022 European Society of Retina Specialists (EURETINA) meeting (1–4 September 2022; virtual and in Hamburg, Germany).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-023-00867-x.

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Mean (95% CI) CST was − 106 (− 114, − 99) µm and − 109 (− 117, − 102) µm at M12 and M24, respectively. At M24, 41.5% of patients had a BCVA ≥ 70 letters. Patients received a mean ± SD of 7.7 ± 2.7 injections by M12 and 10.8 ± 5.0 injections by M24 (3.1 injections between M12 and M24). Adverse events were consistent with the known safety profile of IVT-AFL.

Conclusion: The 24-month results indicate that, in routine clinical practice, a proactive IVT-AFL regimen achieves functional improvements in patients with treatment-naïve nAMD. The proportion of patients achieving ≥ 70 letters at M24 increased, and patients with baseline BCVA ≥ 70 letters maintained vision regardless of the followed IVT-AFL label.

Trial registration: ClinicalTrials.gov identifier: NCT03939767.

Video abstract: A video abstract is available for this article.Supplementary file2 (MP4 364624 KB)

Keywords: Aflibercept; Age-related macular degeneration; Clinical trial; Intravitreal; Macula; Neovascularization; Retina; Vision

Key Summary Points

Why carry out this study?

Patients with neovascular age-related macular degeneration (nAMD) tend to achieve lower visual acuity gains in routine clinical practice than in randomized clinical trials.

The XTEND study is the first study to gather global real-world evidence on proactive intravitreal aflibercept (IVT-AFL) treatment regimens in patients with treatment-naïve nAMD in routine clinical practice and during the COVID-19 pandemic.

What was learned from the study?

Proactive IVT-AFL treatment resulted in meaningful functional and anatomic improvements that were generally maintained across the 24-month analysis period.

The proportion of patients achieving ≥ 70 letters at month 24 increased, and patients with baseline best-corrected visual acuity ≥ 70 letters maintained vision regardless of the followed IVT-AFL label.

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DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24562555.

INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) therapies, such as intravitreal aflibercept (IVT-AFL), ranibizumab, and brolucizumab, have demonstrated robust visual improvements in patients with neovascular age-related macular degeneration (nAMD) [1–6]. However, the outcomes observed in randomized controlled trials (RCTs) are not always realized in routine clinical practice; patients in routine practice tend to receive fewer anti-VEGF injections, particularly after the first year of treatment, and achieve lower visual acuity (VA) gains than typically observed in RCTs [7–10].

While RCTs provide a more controlled environment with selective inclusion criteria, observational studies allow for greater insight into effectiveness and treatment patterns in more heterogeneous populations and elucidate the effects that adherence to and persistence with treatment have on visual outcomes [11]. Thus, real-world evidence (RWE) is valuable to

better understand and address discrepancies in outcomes between RCTs and real-world experience [12–14].

To date, the RWE for IVT-AFL in patients with nAMD has been generated in multicenter, single-country settings: PERSEUS in Germany [15], PERSEUS-IT in Italy [16], and RAINBOW in France [17–19]. Analyses of patient electronic records in the UK have also provided RWE for IVT-AFL [20].

XTEND (eXtended and proacTive dosing regimEn in treatment-Naïve patients with neovascular age-related macular Degeneration) is a multinational, multicenter, observational, prospective study designed to examine the effectiveness of proactive treatment regimens of IVT-AFL following the broadening of the label to include a treat-and-extend (T&E) regimen after the three initial monthly injections in patients with treatment-naïve nAMD. Two IVT-AFL labels are approved for nAMD: the European Medicines Agency (EMA)-aligned label, whereby three monthly injections are followed by a minimum of 8-week intervals in year 1 [21], and the non-EMA-aligned label, whereby the minimum interval is 4 weeks [22]. For both labels, the treatment interval may be extended beyond 2 months after year 1 if specific visual and anatomic criteria are met, thereby balancing injection frequency and associated treatment burden with outcomes.

XTEND is a prospective observational study that assesses the long-term effectiveness, treatment patterns, and safety of IVT-AFL treatment in real-world settings. Here, we report the primary endpoint and 24-month outcomes of XTEND in the ongoing, 36-month XTEND study. Data are presented for the overall population and stratified by IVT-AFL label type. As the COVID-19 pandemic began during the study period, there was an opportunity to reflect on how routine clinical practice with IVT-AFL was impacted. The analyses presented here are explorative and descriptive, and there were no pre-defined hypotheses.

To date, XTEND is the largest, long-term, prospective, observational real-world study of IVT-AFL in treatment-naïve patients with nAMD and aims to generate global insights into opportunities for the optimization of nAMD management in clinical practice. It is the first RWE study to be conducted after the IVT-AFL label was broadened to include a T&E regimen after the three initial monthly injections in patients with nAMD [21, 22].

METHODS

Study Design/Participants

XTEND (ClinicalTrials.gov identifier: NCT03939767) is an ongoing, multinational, multicenter, observational, prospective study examining the effectiveness of real-world proactive treatment regimens of IVT-AFL in patients with treatment-naïve nAMD.

The study is conducted in accordance with guidelines and regulations of the EMA and applicable local law(s) and regulation(s). The protocol and any amendments were reviewed and approved locally by each study independent ethics committee or institutional review board before the start of the study. The study enrolled patients between May 2019 and May 2020, and the patient follow-up period is 36 months.

Patients received IVT-AFL (proactive regimen: fixed dosing or T&E) according to the local label, local standard of care, and judgment of the treating physician. For the T&E regimen, treatment intervals can be extended in 2- to 4-weekly increments to a maximum of 12 or 16 weeks according to the national label—either EMA-aligned or non-EMA-aligned.

In year 1, following three initial monthly injections, the minimum treatment interval was 8 weeks in the EMA-aligned label or 4 weeks in the non-EMA-aligned label. The countries following the EMA-aligned label are Argentina, Belgium, mainland China, Colombia, Denmark, France, Ireland, Italy, Norway, South Korea, Spain, Sweden, Thailand, and the UK; countries following the non-EMA-aligned label are Australia, Canada, and Switzerland.

Ethical Approval

No master Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approval was obtained, as no participating study site was deemed to be the main center for the study. Electronic Supplementary Material (ESM) Table S1 lists the local IRB/IEC committee names and approval numbers in all participating countries, where relevant, under local law. The XTEND study was an observational study in which IVT-AFL was prescribed in the customary manner in accordance with the terms of the marketing authorization. There was no assignment of patients to a particular therapeutic strategy. All treatment decisions fell within current practice, and the prescription of IVT-AFL was clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring evaluations were required for participation in the study. Epidemiological methods were used for the analysis of the collected data.

The XTEND study was conducted in accordance with the Helsinki Declaration of 1964 and the applicable EMA guidelines and local laws and regulations in each country. The recommendations of the European Federation of Pharmaceutical Industries and Associations, European Network of Centers for Pharmacoepidemiology and Pharmacovigilance, Good Pharmacovigilance Practices (GVP module VI), and International Council for Harmonization Guideline E3: Good Clinical Practice were also followed wherever possible. In all countries, where required, the protocol and any amendments were reviewed and approved by each study site's IEC or IRB before and during the study. ESM Table S1 provides the full list of Ethics Approval Boards that approved the study. All patients gave informed consent to participate in the study.

Patients

Male or female patients aged $\geq$ 50 years with nAMD were eligible for enrollment if they were naïve to any treatment, including anti-VEGF therapy. If both of a participant's eyes fulfilled the inclusion criteria, only the eye with the worst VA at baseline was included in the study [21, 22]. Exclusion criteria listed in the national Summary of Product Characteristics included contraindications to IVT-AFL, eye diseases that may require surgery during the observation period in the study eye, or retinal disease that may interfere with treatment of nAMD (see ESM Table S2 for full inclusion and exclusion criteria) [21, 22]. The initial visit, first IVT-AFL 2 mg treatment, follow-up visits, and end-of-observation visit took place according to routine clinical practice and physician choice.

Procedures

The primary endpoint was mean change in best-corrected VA (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline to month 12. The preferred method of measuring BCVA is by ETDRS letters or a Snellen chart with conversion to ETDRS letters. Secondary endpoints included, from baseline: change in BCVA at 24 months; change in BCVA by intended treatment regimen; the proportion of patients with predetermined visual gains and losses (equivalent to 5, 10, and 15 ETDRS letters); the proportion of patients achieving a Snellen equivalent of 20/40 or better; change in central subfield thickness (CST); and injection number. Spectral-domain and time-domain optical coherence tomography were used to measure CST.

The COVID-19 pandemic began after study initiation; therefore, additional COVID-19 sensitivity analyses were performed. The 'pre-COVID-19' group included all patients who received their regular end-of-observation visit before the start date of the COVID-19 pandemic or who received their first injection 180 days prior to their country of residence COVID-19 start date. The pandemic start date (between February and March 2020) was provided by Bayer representatives based on individual national guidelines. The 'during COVID-19' group included all other patients. Differing national guidance in response to the pandemic may have led to changes from the planned proactive treatment regimens.

Safety was assessed throughout the study period. All adverse events (AEs) were summarized using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. AEs were considered to be treatment emergent if they started between the first IVT-AFL injection and 30 days after the last injection. Safety analyses were performed on treatment-emergent AEs (TEAEs); AEs that were not treatment emergent were listed without further analysis.

Statistical Analysis

Statistical analyses were explorative and descriptive, and there were no predefined hypotheses. An overall enrollment target of ≥ 2000 patients (≥ 1200 and ≥ 250 in the EMA-aligned and non-EMA-aligned groups, respectively) was determined by feasibility; this allows for a change from baseline in BCVA letters within a 95% confidence interval (CI) of ± 1.0 letters for the EMA-aligned group and ± 2.2 letters for the non-EMA-aligned group.

All variables were analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e., mean, standard deviation [SD], minimum, median, quartiles, and maximum). Continuous variables are described by absolute value and as change from baseline per analysis time point, if applicable. All analyses were performed by label regimen (countries reflecting the EMA-aligned and the non-EMA-aligned labels). For VA and CST, the last observations were carried forward. Baseline values were not carried forward. Other variables were not imputed. Statistical evaluation was performed by using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA), except when noted otherwise.

Patients who received ≥ 1 IVT-AFL injection were included in the safety analysis set (SAS). Patients were included in the full analysis set (FAS) if they received at least one IVT-AFL injection and had at least one VA measurement with an available BCVA letter score at baseline and at least one post-baseline assessment valid for analysis (i.e., measured ≥ 5 days after an injection). VA and CST outcomes were evaluated at baseline and monthly until month 24.

RESULTS

Patients

At the time of the 24-month analysis, XTEND had enrolled 1561 patients from 127 centers (Fig. 1). A total of 1550 patients were included in the SAS: 1221 (78.8%) patients in the EMA-aligned group and 329 (21.2%) patients in the non-EMA-aligned group. There were 1466 patients (93.9%) included in the FAS: 1165 (79.5%) patients in the EMA-aligned group and 301 (20.5%) patients in the non-EMA-aligned group. Eighty-four patients were excluded from the FAS due to no VA assessment at baseline and/or post baseline.

For the overall population, the mean ± SD age was 78.7 ± 8.5 (range 50–100) years, and 891 patients (60.8%) were female (Table 1). At baseline, the mean ± SD BCVA was 54.3 ± 20.3 letters and the mean ± SD CST was 374 ± 126 µm. Baseline characteristics were similar in both label groups.

Functional Outcomes

For the 1466 patients in the FAS, the mean change in BCVA from baseline (54.3 ± 20.3 letters) was + 4.3 ± 17.6 letters at month 12 and + 2.3 ± 19.5 letters at month 24 (Fig. 2a, b; ESM Table S3). In the EMA-aligned group, the mean (95% CI) change in BCVA was + 4.6 (3.6, 5.6) letters at month 12 and + 2.3 (1.2, 3.4) letters at month 24. In the non-EMA-aligned group, the mean (95% CI) change in BCVA was + 3.4 (1.5, 5.2) letters at month 12 and + 2.2 (0.1, 4.3) letters at month 24.

The mean BCVA changes at months 12 and 24 were numerically highest in patients with a baseline BCVA of < 35 letters (+ 15.1 ± 23.3 letters at month 12 and + 12.3 ± 23.5 letters at month 24). In patients with a baseline BCVA of 35–69 letters, there were improvements of + 4.5 ± 17.6 letters at month 12 and + 2.7 ± 19.6 letters at month 24. In patients with a

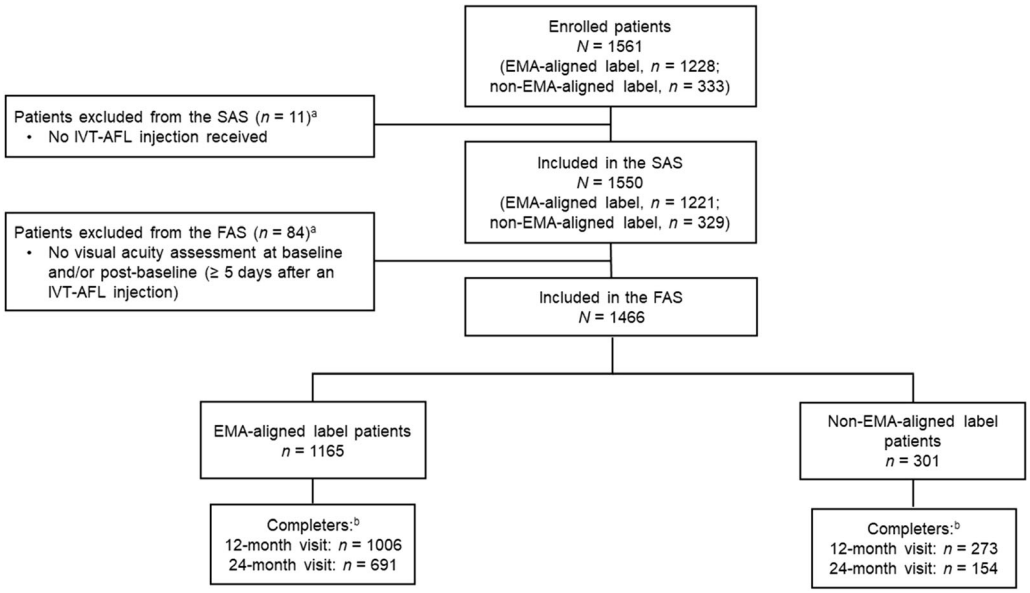


Fig. 1 Patient disposition. [a]Patients could have had more than one reason for exclusion from enrollment. [b]Patients with a visit within the 12-month (360 ± 60 days) or 24-month (720 ± 60 days) visit windows. *EMA* European Medicines Agency, *FAS* full analysis set, *IVT-AFL* intravitreal aflibercept, *SAS* safety analysis set

baseline BCVA of ≥ 70 letters, BCVA was maintained at ≥ 70 letters (month 12, − 0.7 ± 11.6 letters; month 24, − 3.0 ± 14.9 letters) (Fig. 2c).

Of the 1466 patients in the FAS with a BCVA assessment at month 24, 1263 patients (86.2%) maintained vision (i.e., lost ≤ 15 letters). Between baseline and month 24, 731 patients (49.9%) gained ≥ 5 letters; 497 patients (33.9%) gained ≥ 10 letters; 332 patients (22.6%) gained ≥ 15 letters; and 203 patients (13.8%) lost ≥ 15 letters (Fig. 2d). In addition, the proportion of patients with a BCVA ≥ 70 letters was 28.1% (412/1466) at baseline and increased to 41.5% (609/1466) at month 24 (ESM Table S4). There were no marked differences between the letter gains and losses by months 12 and 24, nor between the two label groups (Fig. 2d).

When stratified by intended treatment regimen (T&E or fixed dosing), patients receiving the T&E regimen had a mean ± SD BCVA gain of + 2.6 ± 19.4 letters at month 24, and patients on the fixed dosing regimen had a mean ± SD BCVA gain of 0.0 ± 19.8 letters at month 24.

Anatomic Outcomes

In the overall FAS, mean (95% CI) change in CST from baseline (374 ± 126 μm) was − 106 (− 114, − 99) μm at month 12 and − 109 (− 117, − 102) μm at month 24. Changes at month 24 were numerically similar in both label groups. In the EMA-aligned group, a decrease in CST was achieved by month 12 (mean [95% CI]; − 107 [− 116, − 98] μm) and maintained through to month 24 (− 109 [− 118, − 100] μm); in the non-EMA-aligned group, a similar numerical decrease in CST was achieved by month 12 (− 103 [− 118, − 86] μm) and maintained through to month 24 (− 109 [− 123, − 96] μm; ESM Table S5).

Treatment Patterns and Exposure

For the overall population, the mean ± SD time in study (defined as the mean time between first and last IVT-AFL injections) was 20.0 ± 5.9 months. Patients in the FAS received a mean ± SD of 5.3 ± 1.5 injections by month 6; 7.7 ± 2.7 injections by month 12; and

Table 1 Baseline demographics and disease characteristics in the full analysis set

Characteristic	EMA-aligned label	Non-EMA-aligned label	Total
Number of patients (%)	1165 (100)	301 (100)	1466 (100)
Age, years	78.3 ± 8.6	80.2 ± 8.3	78.7 ± 8.5
Sex, *n* (%)			
Female	705 (60.5)	186 (61.8)	891 (60.8)
Race, *n* (%)[a,b]			
White	676 (58.0)	201 (66.8)	877 (59.8)
Black or African American	2 (0.2)	1 (0.3)	3 (0.2)
Asian	155 (13.3)	15 (5.0)	170 (11.6)
Indigenous	2 (0.2)	2 (0.7)	4 (0.3)
Mixed ancestry	18 (1.5)	3 (1.0)	21 (1.4)
Not reported	52 (4.5)	79 (26.2)	131 (8.9)
Missing	260 (22.3)	0 (0)	260 (17.7)
BCVA, ETDRS letters	55.1 (19.8)	51.6 (21.8)	54.3 (20.3)
CST, μm	378 (131)	362 (107)	374 (126)
BCVA letter score category, *n* (%)			
< 35	139 (11.9)	46 (15.3)	185 (12.6)
≥ 35 to < 70	692 (59.4)	177 (58.8)	869 (59.3)
≥ 70	334 (28.7)	78 (25.9)	412 (28.1)
Primary intended treatment regimen after initial monthly injections, *n* (%)			
Proactive treat-and-extend	999 (85.5)	284 (94.4)	1283 (87.5)
Proactive fixed treatment	166 (14.2)	17 (5.6)	183 (12.5)
Mean time from diagnosis to first IVT-AFL injection, days	40.7 ± 287.4	23.8 ± 159.6	37.2 ± 266.2

Values are presented as the mean ± standard deviation unless otherwise stated

BCVA best-corrected visual acuity, *CST* central subfield thickness, *EMA* European Medicines Agency, *ETDRS* Early Treatment Diabetic Retinopathy Study, *IVT-AFL* intravitreal aflibercept

[a]Data on race were not collected in France

[b]Classified by the investigator using fixed categories, considering information in medical records or provided directly by the patient

10.8 ± 5.0 injections by month 24 (Table 2). In both label groups, the majority of IVT-AFL injections were received by month 12, with a mean increase of 3.1 injections from months 12 to 24. In the EMA-aligned group, patients received a mean ± SD of 7.4 ± 2.6 and 10.5 ± 4.9 injections by months 12 and 24, respectively. In the non-EMA-aligned group, patients received a mean ± SD of 8.6 ± 2.8 and

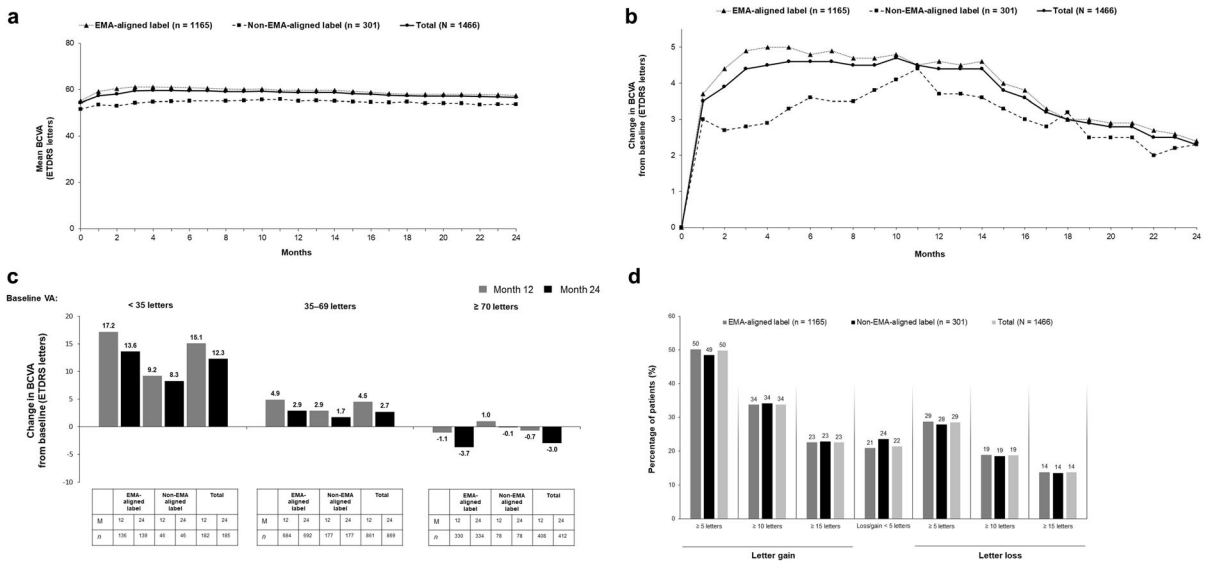


Fig. 2 Visual acuity outcomes in the EMA-aligned label, non-EMA-aligned label, and overall population (FAS, LOCF). **a** Absolute mean BCVA over 24 months. **b** Mean change in BCVA over 24 months. **c** Mean change in BCVA over 24 months stratified by baseline visual acuity. **d** Proportion of patients stratified by BCVA categorical score change over 24 months. Symbols represent mean data. In **a** and **b**, the mean VA change data are based on the nearest VA assessment within the monthly ± 15-day visit windows. *BCVA* best-corrected visual acuity, *EMA* European Medicines Agency, *FAS* full analysis set, *ETDRS* Early Treatment Diabetic Retinopathy Study, *LOCF* last observation carried forward, *M* month, *VA* visual acuity

Table 2 Mean number of intravitreal aflibercept treatments by patient group from baseline to months 6, 12, and 24 in the study eye (full analysis set, observed cases)

Patient groups	Mean number of IVT-AFL treatments		
	BL to month 6	BL to month 12	BL to month 24
EMA-aligned (n = 1165)	5.2 ± 1.4	7.4 ± 2.6	10.5 ± 4.9
Non-EMA-aligned (n = 301)	5.9 ± 1.5	8.6 ± 2.8	12.0 ± 5.2
Total (N = 1466)	5.3 ± 1.5	7.7 ± 2.7	10.8 ± 5.0

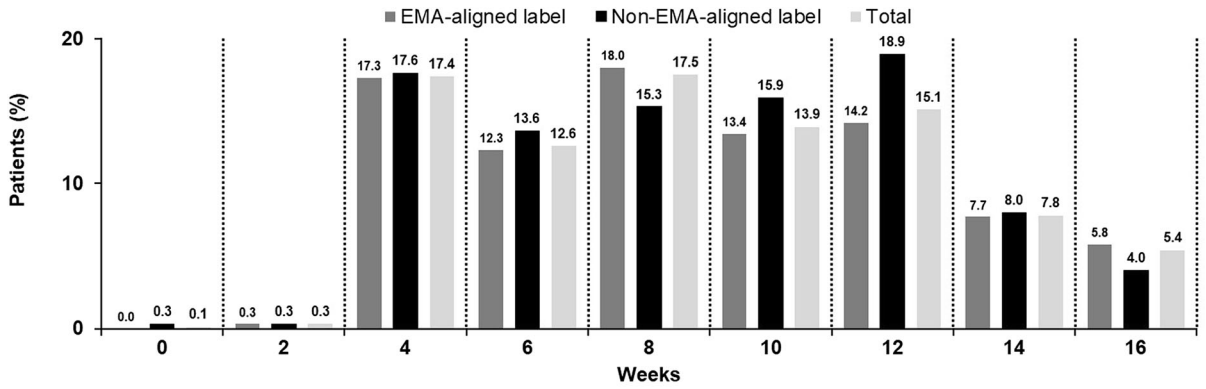
Values are presented as the mean ± standard deviation
BL baseline, *EMA* European Medicines Agency, *IVT-AFL* intravitreal aflibercept

12.0 ± 5.2 injections by months 12 and 24, respectively.

In the overall FAS, the last completed treatment interval was ≥ 12 weeks in 35.6% (522/1466) of patients at month 12 and 37.7% (553/1466) of patients at month 24 (Fig. 3). In the EMA-aligned group, the last completed interval was ≥ 12 weeks in 26.8% (312/1165) of patients at month 12 and 38.0% (442/1165) of patients at month 24. In the non-EMA-aligned group, the last completed interval was ≥ 12 weeks in 20.3% (61/301) of patients at month 12 and 36.5% (110/301) of patients at month 24.

Impact of the COVID-19 Pandemic

For the overall FAS, 1195 and 271 patients were stratified into the 'pre-COVID-19' and 'during COVID-19' groups, respectively; mean baseline BCVA was similar in both groups: 55.3 ± 16.6



Last completed interval up to month 24, *n* (%)	EMA-aligned label *n* = 1165	Non-EMA-aligned label *n* = 301	Total *N* = 1466
≥ 10 weeks	598 (51.3)	158 (52.5)	756 (51.6)
≥ 12 weeks	442 (38.0)	110 (36.5)	552 (37.7)
≥ 16 weeks	187 (16.1)	29 (9.6)	216 (14.7)

Fig. 3 Last completed injection interval up to month 24 (FAS, OC). Data are mean ± SD. *EMA* European Medicines Agency, *FAS* full analysis set, *OC* observed cases, *SD* standard deviation

letters and 54.1 ± 21.1 letters, respectively. The mean (95% CI) BCVA change from baseline at 6 and 12 months was + 5.6 (4.0, 7.2) and + 4.3 (2.5, 6.0) letters, respectively, in the 'pre-COVID-19' group, and + 4.0 (3.0, 4.9) letters and + 4.4 (3.3, 5.4) letters, respectively, in the 'during COVID-19' group. At month 24, the mean (95% CI) change in VA was numerically higher in patients who started treatment during the COVID-19 pandemic (n = 1195; + 2.4 [1.3, 3.6] letters) than pre-COVID-19 (n = 271; + 1.7 [− 0.3, 3.6] letters).

Mean (± SD) baseline CST was comparable in the 'pre-COVID-19' (364 ± 119 μm) and 'during COVID-19' (375 ± 127 μm) groups. The mean CST changes from baseline were numerically similar for the 'pre-COVID-19' and 'during COVID-19' groups at 6 months (n = 168; − 106 ± 126 μm vs. n = 904; − 101 ± 125 μm) and at month 24 (n = 179; − 107 ± 123 μm vs. n = 949; − 109 ± 132 μm). The mean (± SD) numbers of injections for the 'pre-COVID-19' group at 12 and 24 months (n = 271; 7.6 ± 2.5 and 10.9 ± 4.8, respectively) were similar to the 'during COVID-19' group at both time points (n = 1195; 7.8 ± 2.8 and 10.9 ± 5.0, respectively).

Safety

Treatment-emergent AEs were reported in 464 (29.9%) patients of the SAS (ESM Table S6). A total of 325 patients (21.0%) reported ocular TEAEs in either eye, and 233 patients (15.0%) reported any ocular TEAE in the study eye. The most common ocular TEAEs (defined as occurring in ≥ 1% of study eyes) were cataract (43/1550; 2.8%) and blepharitis (19/1550; 1.2%).

In the total population, considering both eyes, 17 cases of intraocular inflammation were reported. Intraocular inflammation was defined by the following preferred terms: eye infection (n = 6), endophthalmitis (n = 3), anterior chamber cell (n = 2), anterior chamber flare (n = 1), anterior chamber inflammation (n = 1), bacterial endophthalmitis (BE; n = 1), iridocyclitis (n = 1), iritis (n = 1), and uveitis (n = 1). All three patients who reported endophthalmitis received IVT-AFL from a vial and were treated with antibiotics. No cases of retinal vasculitis, retinal occlusive vasculitis, or retinal artery occlusion were reported.

DISCUSSION

XTEND is the largest ongoing global study to date to assess proactive IVT-AFL treatment regimens in routine clinical practice in nAMD. Patients with treatment-naïve nAMD receiving IVT-AFL achieved functional and anatomic improvements by month 12 that were maintained at month 24. The mean improvement in BCVA was + 4.3 letters and + 2.3 letters at months 12 and 24, respectively, which is lower than in the VIEW RCT at week 96 (+ 7.6 ETDRS letters [2]). The proportion of patients with BCVA ≥ 70 letters increased from 28.1% at baseline to 41.5% at month 24. This increase is likely due to patients with baseline BCVA < 70 letters having the greatest capacity to improve and IVT-AFL preventing deterioration in patients with BCVA ≥ 70 letters.

Patients also had improvements in CST, although these were not as marked as those reported in key RCTs (– 106 μm and – 109 μm at months 12 and 24, respectively, in XTEND versus – 128 μm at week 96 in VIEW [2]). Even with the relatively low treatment frequency in XTEND compared with VIEW, treatment with IVT-AFL led to improvements by inhibiting fluid accumulation and leakage.

At months 12 and 24 in XTEND, a mean (± SD) 7.7 ± 2.7 and 10.8 ± 5.0 injections, respectively, had been administered, and an average of 3.1 injections were administered from month 12 to 24. The number of injections observed in XTEND was lower than observed in the VIEW RCTs at week 96 (11.2 injections [2]); however, the lower observed injection numbers in the second year of XTEND are consistent with other observational studies of IVT-AFL in nAMD [15, 16, 23]. The results of this analysis indicate that greater visual and anatomic improvements may have been achieved if treatment regimens were more closely aligned to the labels. Data were not stratified according to gender in the XTEND study; IVT-AFL has been commercially available for > 11 years, and, from development until present, there have been no gender-specific effects recorded for IVT-AFL.

XTEND also provides insights into the impact of routine clinical practice on different labels followed globally. The proportion of patients with a last completed interval of ≥ 12 weeks was similar for both groups by 24 months (38.0% for the EMA-aligned label group and 36.5% for the non-EMA-aligned label group), although the injection number was slightly higher in the non-EMA-aligned group at 24 months (12.0 vs. 10.5 in the EMA-aligned group). While similar treatment patterns were observed, the results must be interpreted with caution due to variations from the labels (e.g., shorter treatment intervals), variations from the intended treatment regimen (fixed or T&E), and the variable impact that the COVID-19 pandemic had on healthcare systems.

The safety profile of IVT-AFL over 24 months was consistent with that reported in prior observational studies [15, 17–19, 24]. Three cases of endophthalmitis and one case of BE were observed. BE is a sight-threatening bacterial infection of the interior structures of the eye and is treated through intravitreal or systemic antibiotic injection [25]. Overall, 15,875 injections were observed over 24 months, equating to endophthalmitis affecting one eye per 5292 injections and BE affecting one eye per 15,875 injections.

The strengths of XTEND include the prospective design, long-term study duration, and the large heterogenous population enrolled from 127 centers across 17 countries, with a mean age of patients (78.7 years) that is reflective of patients with nAMD seen in routine clinical practice.

RWE has demonstrated an efficacy gap between outcomes in RCTs and those in routine clinical practice [12–14]. RWE provides valuable understanding on treatment exposure, disease progression, disease burden, and long-term safety [12–14] and is, therefore, more reflective than RCT data of the outcomes patients can expect in routine clinical practice. Regulatory bodies are increasingly using RWE in conjunction with RCT data to inform decision-making [14]. Further, XTEND was conducted before and during the COVID-19 pandemic, providing unique settings from which to generate data from routine clinical practice.

Other large RWE studies of anti-VEGFs have assessed visual outcomes and injection number for nAMD in routine clinical practice (e.g. [26]). While not necessarily employing the T&E regimen as in the XTEND study, these studies nonetheless concur that there is scope for better vison gains if the approved label for anti-VEGFs is more closely followed [26].

Conversely, RWE studies present with limitations inherent in their design. Treatment regimens are standardized based on RCT results [2]; however, these standards are not always applied in clinical practice, and high treatment discontinuation rates and variability in assessment modalities can limit the interpretations made from observational studies [27]. Therefore, the limitations of the XTEND study include the high variability of treatment and monitoring schedules in routine clinical practice according to local guidelines, as these are at the attending physician's discretion. Not all patients attend each of the visits, and not all assessments are conducted each visit, which leads to missing data that may limit the study's interpretations. In addition, the XTEND study took place during the COVID-19 pandemic, and, as per national guidelines or recommendations in some countries, not all patients could be treated as initially intended at the start of the study. Therefore, many patients did not have the opportunity to be extended as rapidly as may have occurred without the pandemic.

CONCLUSION

In the 24-month analysis of XTEND, proactive IVT-AFL treatment resulted in meaningful improvements in BCVA and CST and extended treatment intervals in patients with treatment-naïve nAMD following either the EMA-aligned label or the non-EMA-aligned label. Visual improvements were achieved within the first 12 months and were generally maintained across 24 months during the pandemic.

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Data Availability. Availability of the data underlying this publication will be determined later according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research and Manufacturers of America "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 USA) and

European Union 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 1 January 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.

Declarations

Conflict of Interest. Jean-François Korobelnik has received consulting fees from AbbVie, Apellis, Bayer, Janssen, Nano Retina, Roche, Théa Pharmaceuticals, and Carl Zeiss Meditec AG; and is a member of data safety monitoring boards or advisory boards for Alexion, Novo Nordisk, and Oxular. Varun Chaudhary has received grants from Allergan Inc., Bayer Healthcare, Novartis, and Roche; consulting fees from Allergan-AbbVie, Apellis, Bayer, Care Zeiss Meditec AG, Janssen, Nano Retina, Roche, and Théa Pharmaceuticals; and is a scientific advisor for Alcon Laboratories, Bayer Healthcare, Novartis, and Roche. Paul Mitchell has received consulting fees from Allergan, Apellis, Bayer, Novartis, and Roche; lecture honoraria from Bayer; support for attending meetings and/or travel from Bayer and Roche; and is a member of data safety monitoring boards or advisory boards for Apellis and Bayer. Se Woong Kang has received personal fees and non-financial support from Bayer Korea. Ramin Tadayoni has received consulting fees from Alcon Laboratories, Allergan, Bausch + Lomb, Novartis, Roche, Genentech, and ZEISS; and is a board member for Alcon Laboratories, Alimera Sciences, Allergan, Bausch + Lomb, Bayer, FCI, and Novartis. Helmut Allmeier and Xin Zhang are employees of Bayer Consumer Care AG. Tobias Machewitz and JinKyung Lee are employees of Bayer AG. Clare Bailey has received honoraria from Alimera Sciences, Apellis, Bayer, Boehringer Ingelheim, Janssen, Novartis, and Roche; and is a member of advisory boards for Alimera Sciences, Apellis, Bayer, Boehringer Ingelheim, Janssen, Novartis, and Roche.

Ethical Approval. The XTEND study was conducted in accordance with the Helsinki Declaration of 1964 and the applicable EMA guidelines and local laws and regulations in each country. The recommendations of the European Federation of Pharmaceutical Industries and Associations, European Network of Centers for Pharmacoepidemiology and Pharmacovigilance, Good Pharmacovigilance Practices (GVP module VI), and International Council for Harmonization Guideline E3: Good Clinical Practice were also followed wherever possible. In all countries, where required, the protocol and any amendments were reviewed and approved by each study site's IEC or IRB before and during the study. The full list of Ethics Approval Boards that approved the study is provided in ESM Table 1. All patients gave informed consent to participate in the study.

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