



Real-World Management of Macular Edema Secondary to Retinal Vein Occlusion with Intravitreal Aflibercept: 24-month Results from the AURIGA Observational Study

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ABSTRACT

Introduction: AURIGA is the largest real-world study to date to evaluate intravitreal aflibercept (IVT-AFL) treatment of diabetic macular edema or macular edema secondary to retinal vein occlusion (RVO) in routine clinical practice. Here, we report the 24-month outcomes in the

RVO cohort from France, Germany, Italy, and Taiwan.

Methods: AURIGA (NCT03161912) was a prospective observational study. Eligible patients with RVO were enrolled for whom the decision to treat with IVT-AFL had already been made by the attending physician. Patients were treated with IVT-AFL for up to 24 months at

Former employee: Kay D. Rittenhouse.

Prior Presentation: Data from the global BRVO treatment-naïve cohort of the AURIGA study were presented at EURETINA 2022 (September 1–4, 2022, virtual and in Hamburg, Germany), and data from the global CRVO treatment-naïve cohort were presented at ARVO 2023 (April 23–27, 2023, New Orleans, LA, USA; Abstract #1762). Month-12 data specific to the overall RVO treatment-naïve cohort in France were presented at EURETINA 2021 (September 9–12, 2021, virtual). Month-12 data specific to the overall RVO treatment-naïve country cohort in Taiwan were presented at APRVS 2021 (December 11–12, 2021, virtual). Data specific to the overall RVO treatment-naïve country cohort in Germany were presented at DOG 2022 (September 29–October 2, 2022, Berlin, Germany; Abstract #PDo04-05). Data specific to the overall RVO treatment-naïve country cohort in Taiwan were presented at APRVS 2022 (November 18–20, 2022, virtual and in Taipei City, Taiwan). Data specific to the overall RVO treatment-naïve country cohort in Italy were presented at FLORetina 2022 (December 9–11, 2022, Rome, Italy; Abstract #198). Data specific to the overall RVO treatment-naïve country cohort in France were presented at SFO 2023 (May 6–8, 2023, Paris, France).

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physician discretion according to local practice. The primary endpoint was mean change in visual acuity (VA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from baseline to month (M) 12. All statistical analyses were descriptive.

Results: In 554 treatment-naïve and 65 previously treated patients with RVO, the respective mean (95% confidence interval) change in VA from baseline was + 12.5 (10.8, 14.3) and + 7.9 (3.3, 12.6) letters by M12 and + 11.4 (9.4, 13.3) and + 4.4 (− 0.6, 9.5) letters by M24 (baseline mean ± standard deviation: 51.0 ± 21.9 and 51.9 ± 20.4 letters); 44.0% of treatment-naïve and 27.9% of previously treated patients reported ≥ 15-letter gains by M24. By M24, the mean change in central retinal thickness from baseline was − 247 (− 267, − 227) μm in treatment-naïve patients and − 147 (− 192, − 102) μm in previously treated patients. From baseline to M6, M12, and M24, treatment-naïve patients

received a total of 4.0 ± 1.3 , 5.5 ± 2.5 , and 6.9 ± 4.2 injections, respectively, and previously treated patients received 3.8 ± 1.5 , 5.0 ± 2.2 , and 6.3 ± 3.7 injections, respectively. The safety profile of IVT-AFL was consistent with that of previous studies.

Conclusions: In AURIGA, patients with RVO experienced clinically relevant functional and anatomic improvements following IVT-AFL treatment in routine clinical practice. These improvements were largely maintained in treatment-naïve patients over the 24-month study despite the decreasing treatment frequency, suggesting long-term durability of IVT-AFL treatment outcomes.

Infographic available for this article.

Trial Registration: ClinicalTrials.gov Identifier: NCT03161912 (May 19, 2017).

Infographic:

Real-World Management of Macular Edema Secondary to Retinal Vein Occlusion With Intravitreal Aflibercept: 24-Month Results From the AURIGA Observational Study

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AURIGA STUDY

AURIGA (NCT03161912) was the largest, observational, prospective, multicenter, real-world study to date with intravitreal aflibercept (IVT-AFL) 2 mg treatment in patients with diabetic macular edema (DME) or macular edema secondary to retinal vein occlusion (RVO).

TOTAL ENROLLED RVO PATIENTS

- 562 treatment-naïve.
- 65 pretreated.

Patients were treated with IVT-AFL for up to 24 months at physician's discretion according to local clinical practice.

CONDUCTED IN 11 COUNTRIES IN PATIENTS WITH DME AND RVO

Patients with RVO:

- France (n = 139 treatment-naïve; n = 15 pretreated)
- Italy (n = 152 treatment-naïve; n = 50 pretreated)
- Germany (n = 135 treatment-naïve)
- Taiwan (n = 136 treatment-naïve)
- Lebanon
- Kuwait
- Egypt
- UAE
- Saudi Arabia
- China Mainland
- Russia

WHY IS THIS STUDY IMPORTANT?

RVO is a leading cause of vision loss that affects more than 28 million people worldwide.* Data are needed on long-term treatment outcomes with IVT-AFL in patients with macular edema secondary to RVO.

INCLUSION CRITERIA

Treatment-naïve and pretreated patients aged ≥18 years with RVO for whom the decision to treat with IVT-AFL had already been made by the attending physician.

EXCLUSION CRITERIA

Concomitant therapy with a systemic anti-vascular endothelial growth factor (anti-VEGF), a pro-VEGF agent, or any other agent for the treatment of macular edema secondary to RVO in the study eye.

1 PRIMARY OUTCOME

Mean change (95% CI) in VA from baseline

| Group | MONTH 12 (Primary Endpoint) | MONTH 24 |
|----------------------------------|-----------------------------|---------------------------|
| 554 Treatment-Naïve RVO Patients | +12.5 (10.8, 14.3) letters | +11.4 (9.4, 13.3) letters |
| 65 Pretreated RVO Patients | +7.9 (3.3, 12.6) letters | +4.4 (-0.6, 9.5) letters |

Baseline (mean ± SD): 51.0 ± 21.9 and 51.9 ± 20.4 letters

2 SECONDARY OUTCOMES

Reported ≥15 letter gains

| Group | MONTH 24 |
|------------------------------|----------|
| Treatment-Naïve RVO Patients | 44.0% |
| Pretreated RVO Patients | 27.9% |

Mean change (95% CI) in central retinal thickness from baseline

| Group | MONTH 24 |
|------------------------------|----------------------|
| Treatment-Naïve RVO Patients | -247 (-267, -227) μm |
| Pretreated RVO Patients | -147 (-192, -102) μm |

INJECTIONS (mean ± SD)

| Group | MONTH 6 | MONTH 12 | MONTH 24 |
|------------------------------|-----------|-----------|-----------|
| Treatment-Naïve RVO Patients | 4.0 ± 1.3 | 5.5 ± 2.5 | 6.9 ± 4.2 |
| Pretreated RVO Patients | 3.8 ± 1.5 | 5.0 ± 2.2 | 6.3 ± 3.7 |

The safety profile of IVT-AFL in this study was consistent with that of previous IVT-AFL studies.²⁻⁶

CONCLUSIONS

- In AURIGA, patients with RVO experienced clinically relevant functional and anatomic improvements following IVT-AFL treatment in routine clinical practice.
- These improvements were largely maintained in treatment-naïve patients over the 24-month study despite the decreasing treatment frequency.
 - This suggests long-term durability of IVT-AFL treatment outcomes.

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PEER-REVIEWED FEATURE



The infographic represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

Keywords: Anti-vascular endothelial growth factor; Branch retinal vein occlusion; Central retinal vein occlusion; Intravitreal aflibercept; Macular edema; Observational study; Optical coherence tomography; Real-world evidence; Retinal disease; Retinal vein occlusion

Key Summary Points

Why carry out this study?

Retinal vein occlusion (RVO) is a leading cause of vision loss that affects more than 28 million people worldwide.

Data are needed on long-term treatment outcomes with intravitreal aflibercept (IVT-AFL) in patients with macular edema secondary to RVO.

AURIGA was a 24-month observational study evaluating the effectiveness, treatment patterns, and safety of IVT-AFL in 619 patients with treatment-naïve and previously treated RVO in routine clinical practice in France, Germany, Italy, and Taiwan.

What was learned from this study?

IVT-AFL treatment resulted in robust and clinically relevant functional and anatomic improvements that were largely maintained across the study period, even with reduced treatment frequency after the first 6 months.

The findings of AURIGA indicate that IVT-AFL is effective in the real-world treatment of macular edema secondary to RVO, although greater visual acuity gains may have been achieved with more frequent treatment within the first year.

understanding of the article. To view digital features for this article go to: <https://doi.org/10.6084/m9.figshare.24219886>.

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal cause of vision loss after diabetic retinopathy, affecting more than 28 million people globally with a similar prevalence in males and females [1]. RVO is an obstruction of the retinal venous system that is broadly classified as either branch RVO (BRVO) or central RVO (CRVO) based on the site of occlusion. Although CRVO is approximately five-fold less prevalent than BRVO [1], it is associated with more severe vision loss [2–4].

In patients with RVO, macular edema is a common complication and the leading cause of vision loss [5]. Multiple factors are involved in the pathogenesis of RVO and the associated macular edema, including vascular endothelial growth factors (VEGF) [6, 7]. When capillary blood flow in the retina is occluded, the aqueous and vitreous levels of mediators such as VEGF and placental growth factor become elevated in response. This in turn promotes pathologic capillary permeability and the subsequent development of macular edema. Intravitreal anti-VEGF therapies such as aflibercept and ranibizumab were developed to target this pathomechanism and have since become the standard of care for treating RVO [6].

The efficacy and safety of intravitreal anti-VEGF therapies in the treatment of RVO have been evaluated in several key randomized controlled trials (RCTs) [6]. The key RCTs in the regulatory approval of ranibizumab for BRVO and CRVO were BRAVO and CRUISE, respectively [10, 11]. Intravitreal aflibercept (IVT-AFL) was approved for CRVO based on the GALILEO [12–15] and COPERNICUS [12, 16–18] studies, and it was subsequently approved for the treatment of BRVO based on the VIBRANT study [19, 20]. Whereas ranibizumab treatment of RVO has been evaluated in various studies of between 2 and 5 years in duration, robust long-term data on IVT-AFL are still needed, particularly in the treatment of BRVO [5].

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate

Observational studies produce key, real-world evidence (RWE) not only on the effectiveness and long-term safety of therapies, but also on other factors such as treatment patterns, disease progression, disease burden, and patient-reported outcomes [21–23]. In RCTs, patients are enrolled according to specific criteria and there are strict treatment protocols. In contrast, RWE is typically gathered from more heterogeneous patient cohorts (including patients with relevant comorbidities) who are treated according to physician discretion. RWE can, therefore, provide important insights pertinent to the management of disease in routine clinical practice. Currently, limited RWE is available regarding the use of IVT-AFL in the treatment of RVO [5].

The AURIGA study (NCT03161912) was a prospective observational study that evaluated the long-term effectiveness, treatment patterns, safety, and patient-reported outcomes of IVT-AFL treatment outside of RCT settings. Here, we report the primary endpoint and final, 24-month outcomes of AURIGA in treatment-naïve and previously treated patients with macular edema secondary to RVO. AURIGA was the first large-scale, real-world study of IVT-AFL treatment in these patients, and the goal of the study was to gain robust insights to help guide the future clinical management of this disease.

METHODS

Study Design

AURIGA (NCT03161912) was a 24-month, prospective, multinational, observational study to assess the real-world effectiveness, treatment patterns, and safety of IVT-AFL in treatment-naïve and previously treated patients with diabetic macular edema (DME) or macular edema secondary to RVO. Across both indications, the study enrolled a total of 2529 patients from 243 eye clinics and ophthalmology practices in 11 countries between November 24, 2017, and December 17, 2021. All treatment and monitoring decisions, including the initial decision to treat with IVT-AFL, were made by the attending physician according to their local

practice and local marketing authorization. Sample size was calculated to enable sufficient precision in the assessment of the primary endpoint (mean change in visual acuity [VA] from baseline to month 12) by country and by cohort, and this resulted in a planned enrollment of 540 and 270 patients with treatment-naïve and previously treated RVO, respectively (see Supplementary Methods in the electronic supplementary material for details).

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. Appendix I in the Supplementary Materials lists the local IRB/IEC committee names and approval numbers in all participating countries where relevant under local law. The AURIGA 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 AURIGA study was conducted in accordance with the Helsinki Declaration of 1964 and the applicable European Medicines Agency (EMA) guidelines and local laws and regulations in each country. The recommendations of the European Federation of Pharmaceutical Industries and Associations (EFPIA), European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP), Good Pharmacovigilance Practices (GVP module VI), and the 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 independent ethics committee or institutional review board before and during the study. All patients provided written informed consent for participation in this study.

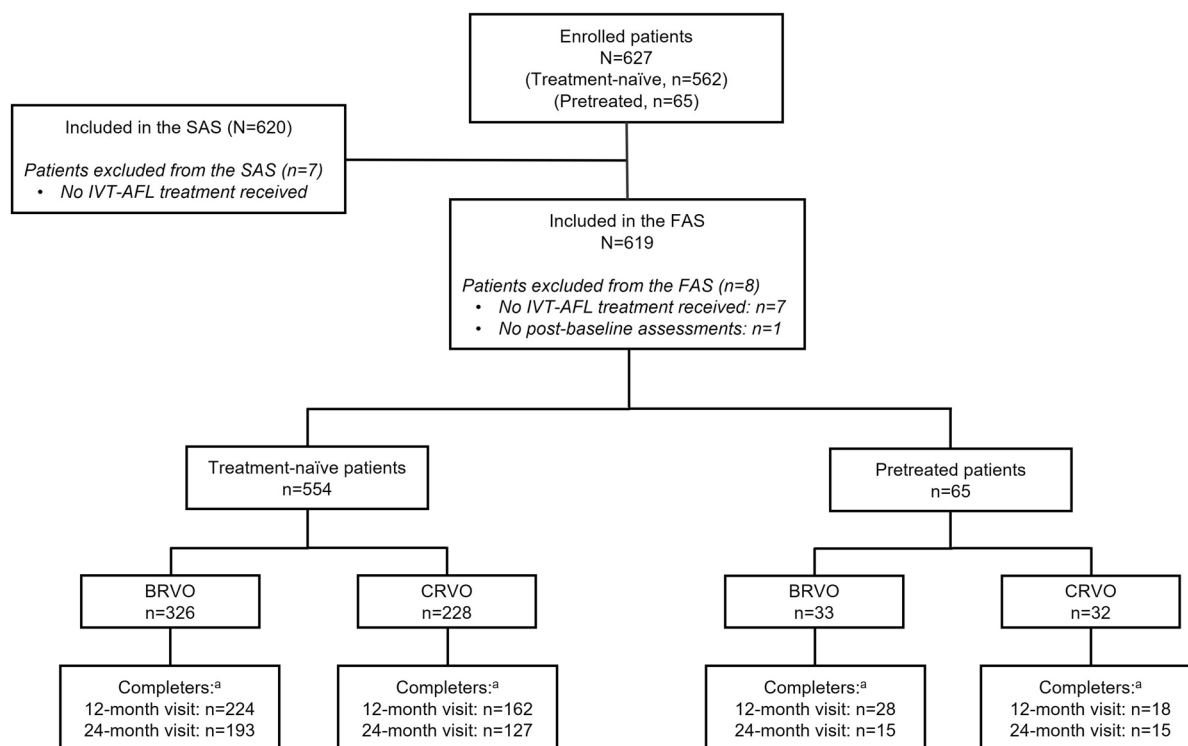


Fig. 1 Patient disposition. ^aAll patients who received an IVT-AFL treatment within ± 60 days of the 12-/24-month visit window. *BRVO* branch retinal vein occlusion,

CRVO central retinal vein occlusion, *FAS* full analysis set, *IVT-AFL* intravitreal aflibercept, *SAS* safety analysis set

Patients and Procedures

Four countries contributed toward the overall RVO cohort, namely France, Germany, Italy, and Taiwan. The key inclusion criteria were treatment-naïve and previously treated patients aged ≥ 18 years with macular edema secondary to RVO for whom the decision to treat with IVT-AFL had already been made by the attending physician according to local clinical practice. In the previously treated cohort, only patients who had received prior treatment with steroids or intravitreal anti-VEGF agents other than IVT-AFL were eligible for enrollment. Exclusion criteria are listed in the Supplementary Methods.

As AURIGA was an observational study with the aim of assessing IVT-AFL real-world treatment practices, effectiveness, and safety, there were no prespecified treatment or retreatment criteria. All treatment and monitoring decisions were made at the discretion of the attending

physician with consideration of the local IVT-AFL Summary of Product Characteristics (SmPC), and all treatments, visual acuity measurements, and anatomic assessments were performed according to routine clinical practice at each study site.

Visual outcomes were preferably assessed using best-corrected visual acuity (BCVA) as evaluated with Early Treatment Diabetic Retinopathy Study (ETDRS) charts; where ETDRS charts were unavailable, BCVA was evaluated using other methods (e.g., Snellen charts). In regions where BCVA was not part of the standard of care, conventional VA measurements were conducted and the data were later converted into ETDRS letter scores for statistical analysis [24]. Central retinal thickness (CRT) was measured by time-domain or spectral-domain optical coherence tomography (SD-OCT) using the instrument available at each site, and data generated by time-domain optical coherence tomography were converted to SD-

Table 1 Baseline demographics and disease characteristics

| | BRVO treatment- naïve (n = 326) | CRVO treatment- naïve (n = 228) | Overall RVO treatment-naïve (N = 554) | BRVO previously treated (n = 33) | CRVO previously treated (n = 32) | Overall RVO previously treated (N = 65) |
|--|--|--|--|---|---|--|
| Patient demographics | | | | | | |
| Age, years | 67.2 ± 12.4 | 68.7 ± 13.3 | 67.8 ± 12.8 | 72.7 ± 10.0 | 72.0 ± 12.5 | 72.4 ± 11.2 |
| Male, n (%) | 174 (53.4) | 125 (54.8) | 299 (54.0) | 14 (42.4) | 17 (53.1) | 31 (47.7) |
| Race, n (%) ^a | | | | | | |
| Asian | 93 (37.5) | 41 (24.8) | 134 (32.4) | 0 | 0 | 0 |
| Black | 1 (0.4) | 0 | 1 (0.2) | 0 | 1 (4.8) | 1 (2.0) |
| White | 154 (62.1) | 124 (75.2) | 278 (67.3) | 29 (100) | 20 (95.2) | 49 (98.0) |
| Missing, n ^b | 78 | 63 | 141 | 4 | 11 | 15 |
| Time from RVO diagnosis to first IVT-AFL treatment, months | | | | | | |
| Mean | 1.2 ± 4.9 ^c | 1.0 ± 4.0 | 1.1 ± 4.6 ^c | 29.6 ± 26.9 | 14.9 ± 18.9 | 22.3 ± 24.3 |
| Median | 0.3 ^c | 0.3 | 0.3 ^c | 23.7 | 8.2 | 11.1 |
| Visual characteristics | | | | | | |
| VA, letters | 54.7 ± 19.6 | 45.5 ± 23.8 | 51.0 ± 21.9 | 57.2 ± 15.5 | 46.0 ± 23.6 | 51.9 ± 20.4 |
| Missing, n | 8 | 9 | 17 | 0 | 2 | 2 |
| VA categories, n (%) ^a | | | | | | |
| < 35 letters | 38 (11.9) | 60 (27.4) | 98 (18.2) | 3 (9.1) | 7 (23.3) | 10 (15.9) |
| 35–69 letters | 190 (59.7) | 118 (53.9) | 308 (57.4) | 19 (57.6) | 17 (56.7) | 36 (57.1) |
| ≥ 70 letters | 90 (28.3) | 41 (18.7) | 131 (24.4) | 11 (33.3) | 6 (20.0) | 17 (27.0) |
| Anatomic characteristics | | | | | | |
| CRT, μm | 506 ± 163 | 626 ± 209 | 555 ± 192 | 421 ± 120 | 524 ± 169 | 467 ± 151 |
| Missing, n | 38 | 29 | 67 | 1 | 6 | 7 |
| SRF present, n (%) ^a | 105/210 (50.0) | 85/147 (57.8) | 190/357 (53.2) | 7/30 (23.3) | 13/23 (56.5) | 20/53 (37.7) |
| Missing, n | 116 | 81 | 197 | 3 | 9 | 12 |
| IRF present, n (%) ^a | 204/212 (96.2) | 144/153 (94.1) | 348/365 (95.3) | 28/30 (93.3) | 23/24 (95.8) | 51/54 (94.4) |
| Missing, n | 114 | 75 | 189 | 3 | 8 | 11 |

Data are mean ± SD unless otherwise stated

BRVO branch RVO, CRT central retinal thickness, CRVO central RVO, IRF intraretinal fluid, IVT-AFL intravitreal aflibercept, RVO retinal vein occlusion, SD standard deviation, SRF subretinal fluid, VA visual acuity

^aProportions calculated based on the number of patients with data available at baseline

^bFrance does not allow the collection of race data in clinical studies

^cData from three patients were missing from the BRVO treatment-naïve cohort

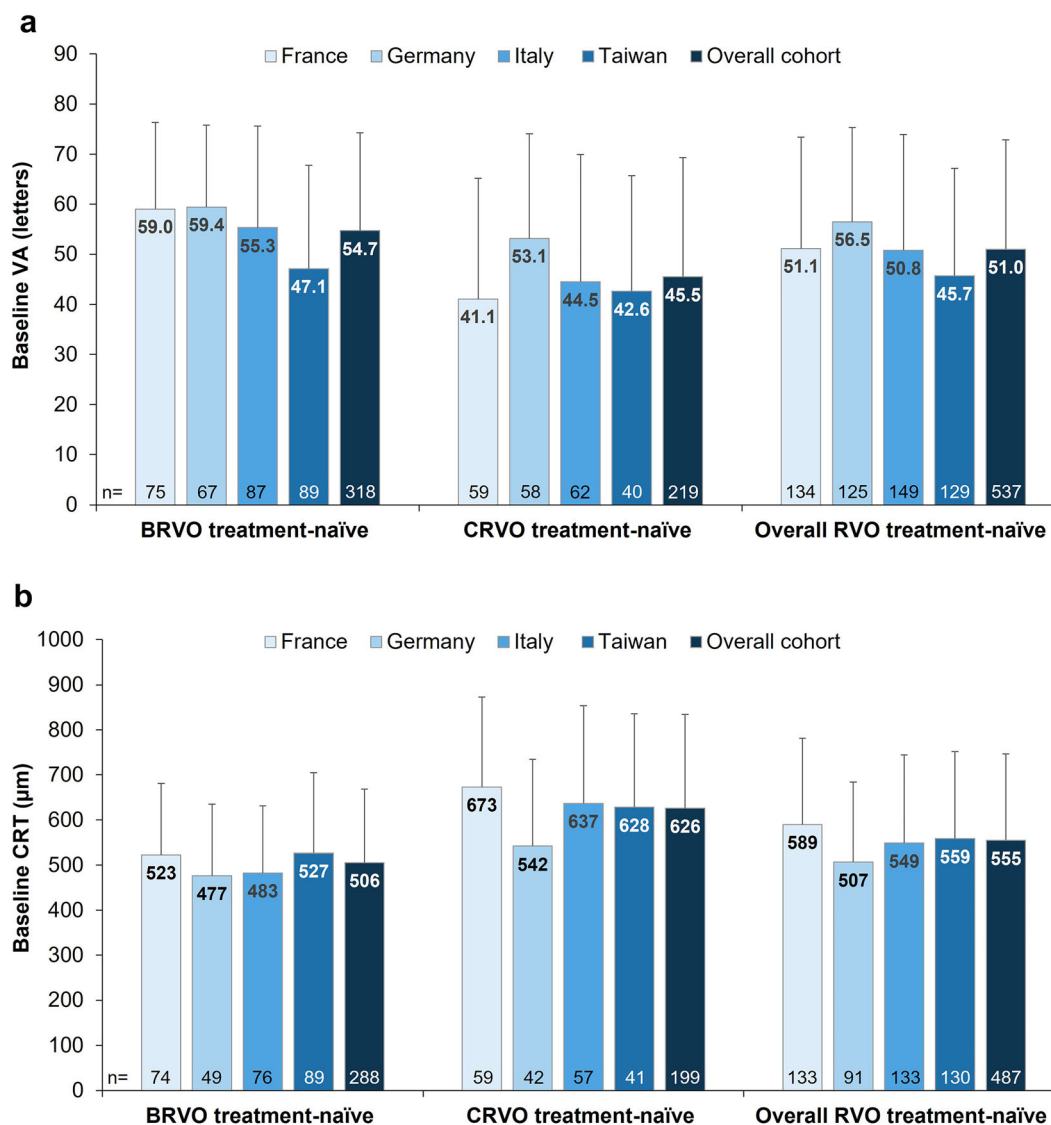


Fig. 2 Mean baseline VA **a** and CRT **b** in the four countries contributing toward the RVO treatment-naïve cohorts. *BRVO* branch retinal vein occlusion, *CRT* central

retinal thickness, *CRVO* central retinal vein occlusion, *RVO* retinal vein occlusion, *VA* visual acuity

OCT measurements for later analysis [25]. Fluid persistence was assessed using SD-OCT and the results were interpreted locally at the study site.

Study Endpoints

The study endpoints were assessed using data for each patient in the full analysis set (FAS) from visits closest to month 6 (150–210 days after baseline), month 12 (300–420 days after

baseline), and month 24 (660–794 days after baseline). The FAS comprised all patients who received ≥ 1 IVT-AFL injection within the study period and who underwent ≥ 1 observation post-baseline.

The primary endpoint of AURIGA was the mean change in VA from baseline to month 12. Secondary endpoints included the proportion of patients with prespecified VA gains and losses, mean change in CRT from baseline,

Table 2 Mean change in visual acuity (letters) from baseline to months 6, 12, and 24

| | BRVO treatment-naïve (n = 326) | CRVO treatment-naïve (n = 228) | Overall RVO treatment-naïve (N = 554) | BRVO previously treated (n = 33) | CRVO previously treated (n = 32) | Overall RVO previously treated (N = 65) |
|-----------------|---------------------------------------|---------------------------------------|--|---|---|--|
| Baseline | | | | | | |
| Mean VA | 54.7 ± 19.6 | 45.5 ± 23.8 | 51.0 ± 21.9 | 57.2 ± 15.5 | 46.0 ± 23.6 | 51.9 ± 20.4 |
| n, % | 318 (97.5) | 219 (96.1) | 537 (96.9) | 33 (100) | 30 (93.8) | 63 (96.9) |
| Month 6 | | | | | | |
| Change from BL | 13.4 (11.5, 15.3) | 10.7 (7.4, 13.9) | 12.3 (10.5, 14.0) | 2.3 (- 4.9, 9.5) | 6.7 (- 2.1, 15.5) | 4.3 (- 1.1, 9.8) |
| n, % | 296 (90.8) | 208 (91.2) | 504 (91.0) | 30 (90.9) | 26 (81.3) | 56 (86.2) |
| Month 12 | | | | | | |
| Change from BL | 13.9 (12.0, 15.8) | 10.5 (7.3, 13.8) | 12.5 (10.8, 14.3) | 5.8 (- 0.1, 11.8) | 10.3 (2.6, 18.0) | 7.9 (3.3, 12.6) |
| n, % | 302 (92.6) | 210 (92.1) | 512 (92.4) | 32 (97.0) | 28 (87.5) | 60 (92.3) |
| Month 24 | | | | | | |
| Change from BL | 13.2 (11.0, 15.4) | 8.8 (5.3, 12.2) | 11.4 (9.4, 13.3) | 2.3 (- 4.4, 8.9) | 6.8 (- 1.2, 14.8) | 4.4 (- 0.6, 9.5) |
| n, % | 303 (92.9) | 211 (92.5) | 514 (92.8) | 32 (97.0) | 29 (90.6) | 61 (93.8) |

Data are from the FAS (LOCF) and values are mean ± SD and mean (95% CI) unless otherwise stated. The mean VA change data are based on the nearest VA assessment within the ± 30-day visit window at 6 months and within the ± 60-day visit window at month 12 and month 24
 BL baseline, BRVO branch RVO, CI confidence interval, CRVO central RVO, FAS full analysis set, LOCF last observation carried forward, RVO retinal vein occlusion, SD standard deviation, VA visual acuity

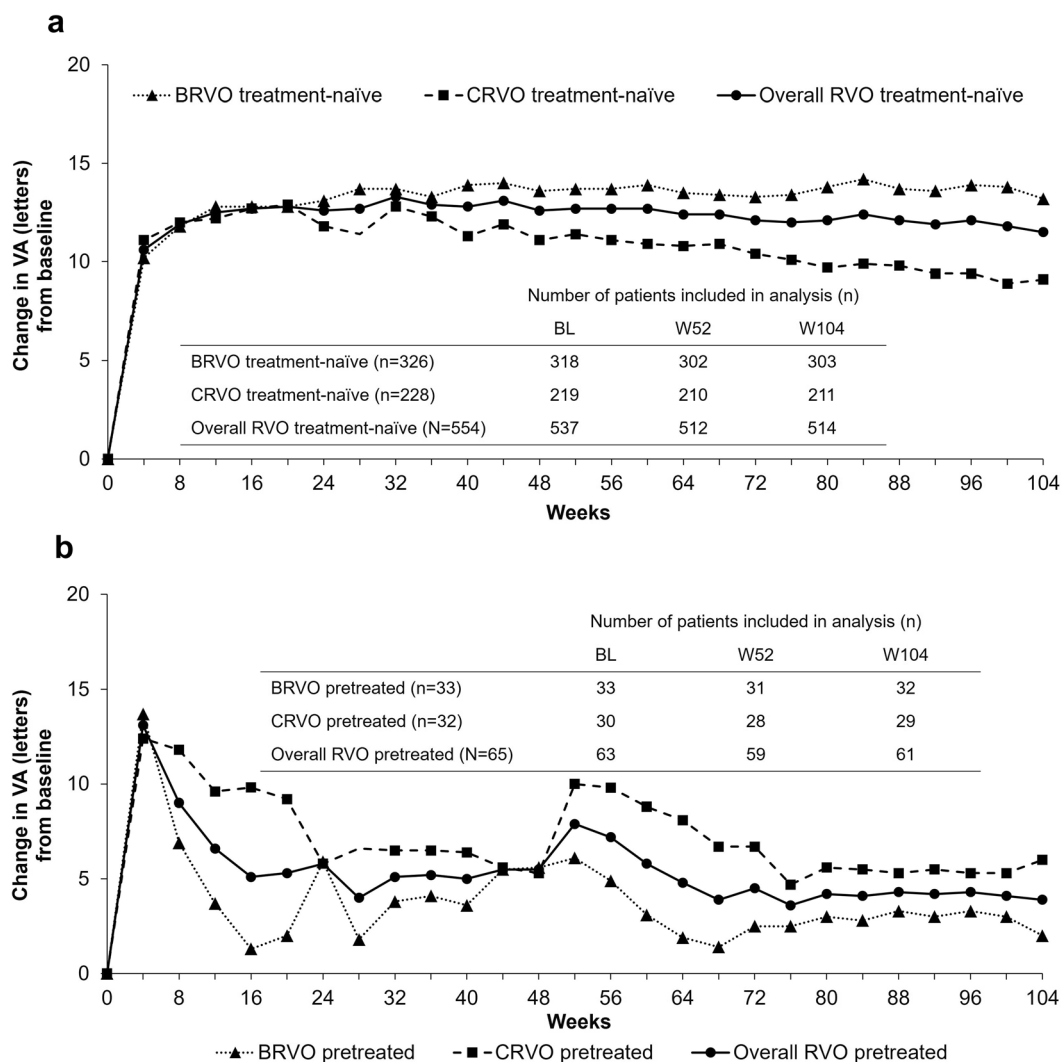


Fig. 3 Mean change in VA (LOCF) over 24 months in patients with **a** treatment-naïve and **b** previously treated macular edema secondary to RVO. Patients were treated for up to 24 months with intravitreal aflibercept in routine clinical practice. The mean VA change data reported here are based on the nearest VA assessments within the +

14/ – 13-day visit windows at 4-week (28-day) intervals. *BL* baseline, *BRVO* branch retinal vein occlusion, *CRVO* central retinal vein occlusion, *LOCF* last observation carried forward, *RVO* retinal vein occlusion, *VA* visual acuity, *W* week

presence of retinal fluid, mean number of injections received, mean time in study, and mean number of visits of each type. All endpoints were assessed at months 6, 12, and 24. To evaluate the trend in VA and CRT over time, data collected for the FAS throughout the study were also analyzed at 4-weekly intervals (every 28 days) within a time window of + 14/ – 13 days. Further evaluations included a sensitivity

analysis of the impact of the Coronavirus Disease 2019 (COVID-19) pandemic on study outcomes, and an exploratory analysis of the impact of IVT-AFL treatment on resource usage and health-related quality of life.

For the COVID-19 sensitivity analysis, the “pre-COVID” group included all patients who received their first IVT-AFL injection at least 360 days prior to the COVID-19 start date in the

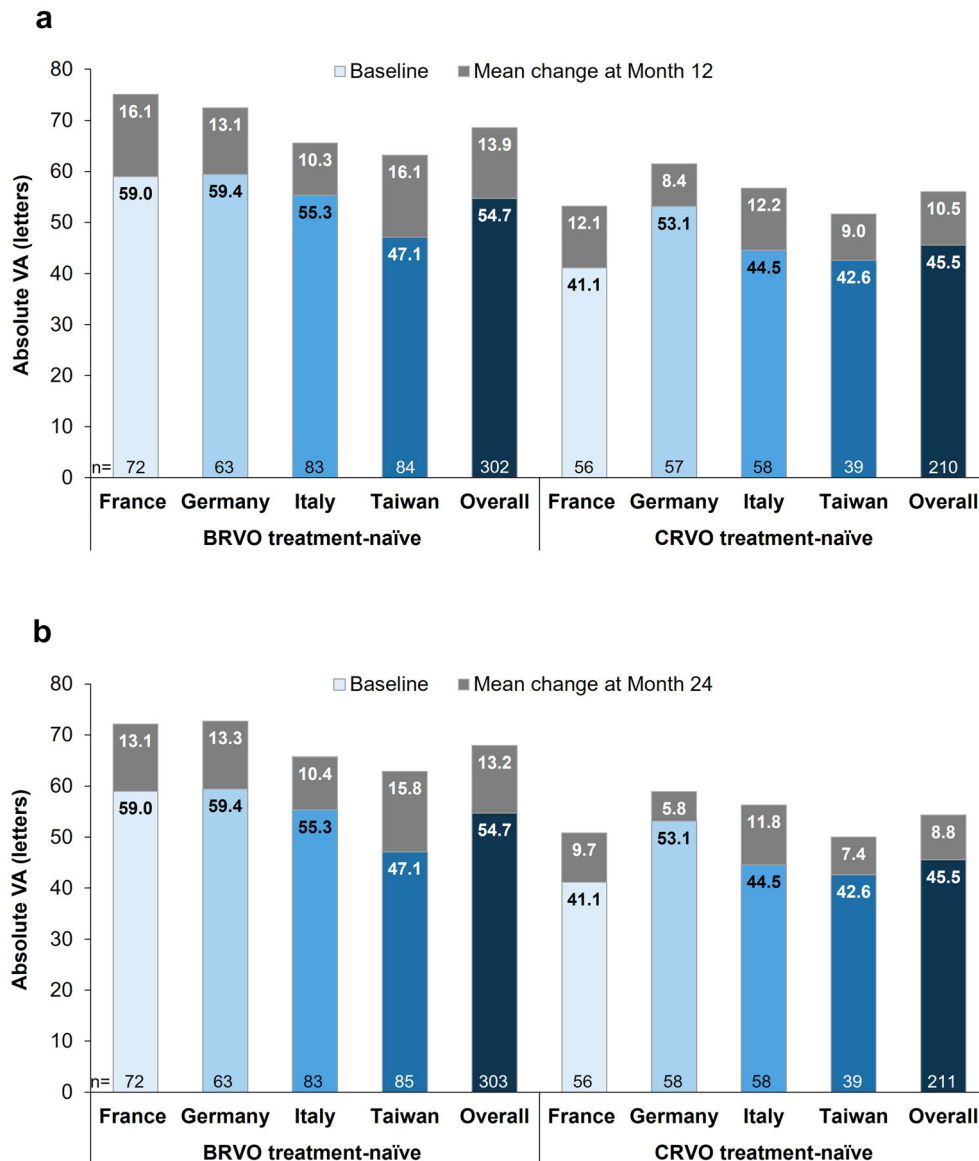


Fig. 4 Mean change in VA (LOCF) from baseline to **a** month 12 and **b** month 24 in the four countries contributing toward the overall RVO treatment-naïve cohort. *N* values represent the number of patients included

in the analysis at month 12 (**a**) and month 24 (**b**). *BRVO* branch retinal vein occlusion, *CRVO* central retinal vein occlusion, *LOCF* last observation carried forward, *RVO* retinal vein occlusion, *VA* visual acuity

country in which they resided, and the “during COVID” group included all other patients. The country COVID-19 start date was the date on which ≥ 100 confirmed COVID-19 cases were reported for that country. The COVID-19 start dates for France, Germany, Italy, and Taiwan were February 29, March 1, February 23, and March 18, 2020, respectively.

Only data from the study eye of each patient were used to evaluate the primary and secondary endpoints. The study eye was defined as the eye in which IVT-AFL treatment was initiated; where treatment began simultaneously in both eyes, the study eye was the one with the worst VA at baseline.

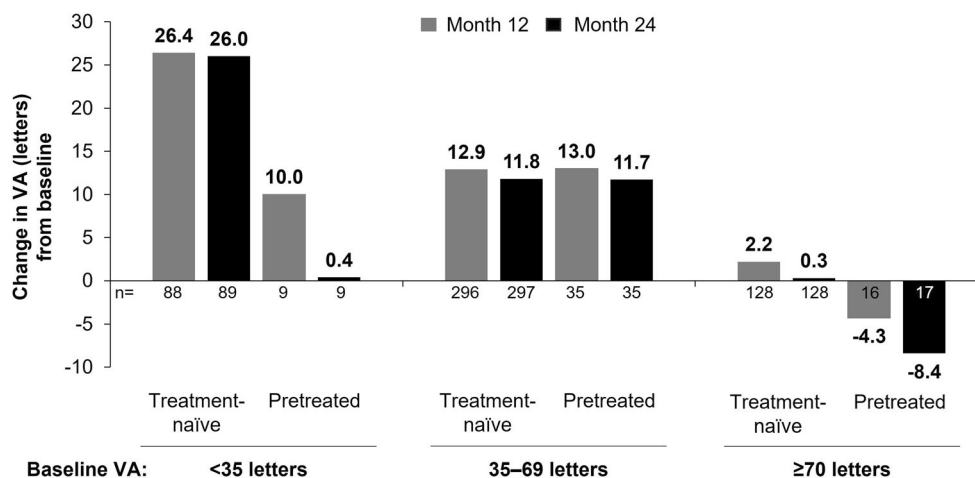


Fig. 5 Mean change in VA (LOCF) from baseline to months 12 and 24 following intravitreal aflibercept treatment in patients with RVO stratified by baseline

visual acuity. *LOCF* last observation carried forward, *RVO* retinal vein occlusion, *VA* visual acuity

Safety was assessed throughout the study and the safety analysis set (SAS) comprised all patients who received ≥ 1 IVT-AFL injection within the study period. Ocular adverse events were reported for the study eye, as well as the fellow eye in patients who received IVT-AFL treatment in both eyes. All treatment-emergent adverse events (TEAEs) were summarized using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were considered treatment-emergent if they started after the first IVT-AFL injection or, at most, 30 days after the last injection.

Statistical Analysis

Statistical analyses were of an explorative and descriptive nature, and the study did not aim to confirm or reject pre-defined hypotheses. The data were analyzed descriptively by presenting frequency distributions, percentages, and summary statistics per cohort by country, as well as overall (pooled). For analyses of the mean change in VA and CRT from baseline to each of the study time points, the 95% confidence interval (CI) was calculated, and any missing data were imputed using the last observation carried forward (LOCF) method; however, baseline VA and CRT measurements were never carried forward. The LOCF imputation was not

applied to the analysis of any other endpoints. All statistical analyses were performed using the Statistical Analysis System software v9.4 or higher (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

In total, 562 treatment-naïve patients and 65 previously treated patients with macular edema secondary to RVO were enrolled in the AURIGA study (Fig. 1). Four of the 11 participating countries contributed toward the global AURIGA RVO cohort: treatment-naïve patients were enrolled from France ($n = 139$), Germany ($n = 135$), Italy ($n = 152$), and Taiwan ($n = 136$), whereas previously treated patients were enrolled from France ($n = 15$) and Italy ($n = 50$). The SAS and FAS comprised almost all the 562 treatment-naïve patients enrolled (98.8% and 98.6%, respectively) and all 65 of the previously treated patients enrolled. Overall, 56.9% ($n = 37$) of previously treated patients in the FAS had switched to IVT-AFL due to persistent retinal fluid (intraretinal or subretinal fluid), followed by 29.2% ($n = 19$) who switched to IVT-AFL due to the recurrence of retinal fluid (Table S1).

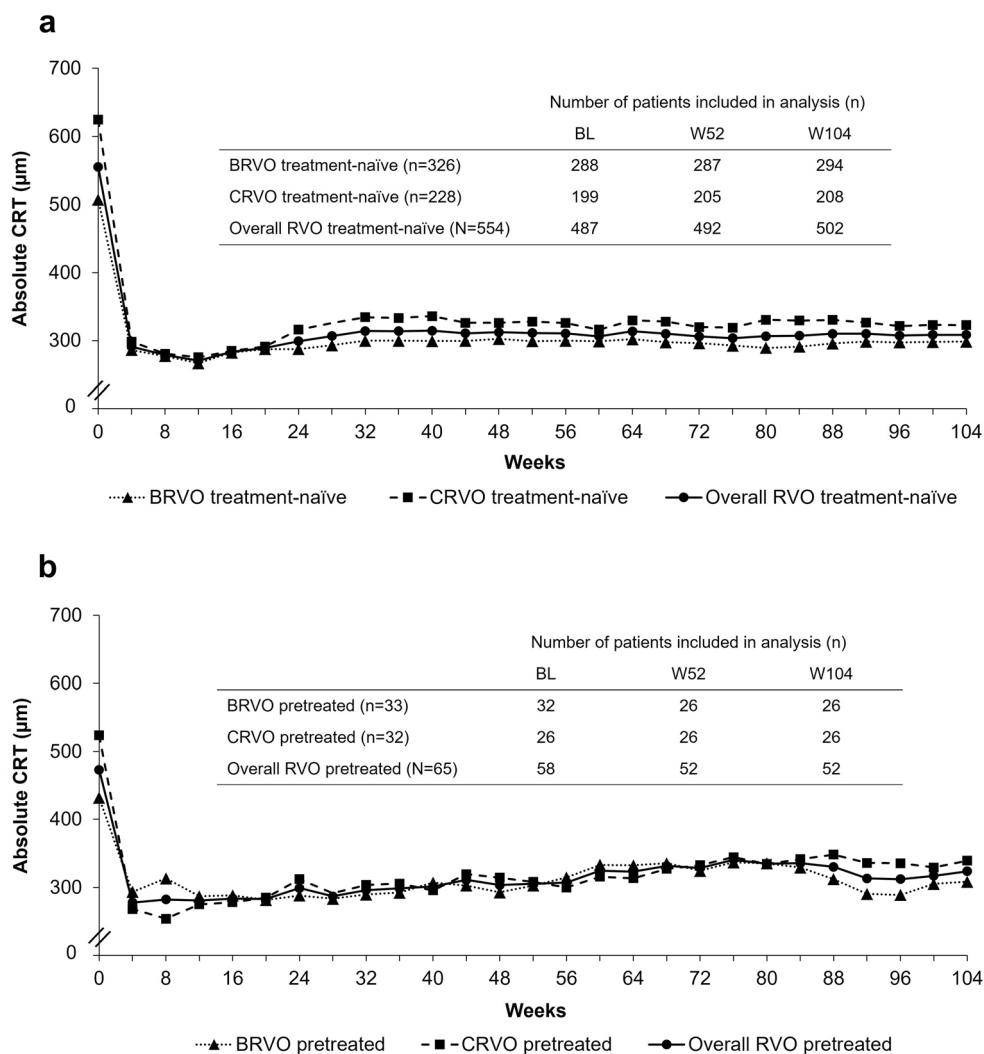


Fig. 6 Absolute mean CRT over 24 months in patients with **a** treatment-naïve and **b** previously treated macular edema secondary to RVO. The CRT data reported here are based on the nearest OCT assessments within the +14/−13-day visit windows at 4-week intervals.

The baseline demographics and disease characteristics of the patients in the FAS are listed in Table 1. In the overall RVO treatment-naïve cohort, the mean age was 67.8 years (25–95 years), 54.0% were male, the mean baseline VA was 51.0 ± 21.9 letters, and the mean baseline CRT was 555 ± 192 μm . These baseline characteristics were similar in the overall RVO previously treated cohort: mean age of 72.4 years (38–93 years), 47.7% were male, the mean baseline VA was 51.9 ± 20.4

BL baseline, *BRVO* branch retinal vein occlusion, *CRT* central retinal thickness, *CRVO* central retinal vein occlusion, *OCT* optical coherence tomography, *RVO* retinal vein occlusion, *W* week

letters, and the mean baseline CRT was 467 ± 151 μm . The median duration between RVO diagnosis and the first IVT-AFL treatment was 0.3 months in the treatment-naïve cohort and 11.1 months in the previously treated cohort. There were no marked differences among the participating countries in terms of baseline demographics except for race (data not shown) and time from diagnosis to first treatment (Table S2). There was some variation in baseline VA and CRT among the different

Table 3 Mean number of IVT-AFL treatments in each treatment cohort

| Cohort | BL to month 6 IVT-AFL treatments | BL to month 12 | BL to month 24 |
|---------------------------|-------------------------------------|----------------|----------------|
| Treatment-naïve | | | |
| BRVO ($n = 326$) | 3.9 ± 1.3 | 5.2 ± 2.5 | 6.5 ± 4.0 |
| CRVO ($n = 228$) | 4.1 ± 1.3 | 5.8 ± 2.6 | 7.4 ± 4.3 |
| Overall RVO ($N = 554$) | 4.0 ± 1.3 | 5.5 ± 2.5 | 6.9 ± 4.2 |
| Previously treated | | | |
| BRVO ($n = 33$) | 3.7 ± 1.5 | 5.1 ± 2.3 | 6.4 ± 3.7 |
| CRVO ($n = 32$) | 3.8 ± 1.4 | 5.0 ± 2.0 | 6.3 ± 3.8 |
| Overall RVO ($N = 65$) | 3.8 ± 1.5 | 5.0 ± 2.2 | 6.3 ± 3.7 |

Values are mean \pm SD. Note that means are calculated across all patients in the FAS and not only for patients completing a visit at each of the indicated time points

BL baseline, BRVO branch RVO, CRVO central RVO, FAS full analysis set, IVT-AFL intravitreal aflibercept, RVO retinal vein occlusion, SD standard deviation

countries, as illustrated by the treatment-naïve patients in Fig. 2.

Functional Outcomes

The mean baseline VA of the CRVO treatment-naïve and previously treated cohorts (45.5 ± 23.8 and 46.0 ± 23.6 letters, respectively) was lower than that of the BRVO treatment-naïve and previously treated cohorts (54.7 ± 19.6 and 57.2 ± 15.5 letters, respectively; Table 2). In terms of the primary endpoint, the mean (95% CI) change in VA from baseline to month 12 was +12.5 (10.8, 14.3) letters for the overall RVO treatment-naïve cohort (+13.9 [12.0, 15.8] letters for BRVO and +10.5 [7.3, 13.8] letters for CRVO) and +7.9 (3.3, 12.6) letters for the overall RVO previously treated cohort (+5.8 [−0.1, 11.8] letters for BRVO and +10.3 [2.6, 18.0] letters for CRVO). The primary outcome stratified by gender is provided in Table S3. In the BRVO treatment-naïve cohort, there was a rapid increase in mean VA with a robust gain of +13.4 (11.5, 15.3) letters by month 6. This gain was maintained through month 12 (+13.9 [12.0, 15.8] letters) to month 24 (+13.2 [11.0, 15.4] letters); in the CRVO treatment-naïve cohort, a similarly robust increase in mean VA

was achieved by month 6 (+10.7 [7.4, 13.9] letters) and was maintained at month 12 (+10.5 [7.3, 13.8] letters), with a slight decrease observed at month 24 (+8.8 [5.3, 12.2] letters). In the BRVO and CRVO previously treated cohorts, markedly smaller increases in mean VA were achieved by month 6 (+2.3 [−4.9, 9.5] and +6.7 [−2.1, 15.5] letters, respectively), with further gains observed by month 12 (+5.8 [−0.1, 11.8] and +10.3 [2.6, 18.0] letters, respectively) and a return to month 6 levels by month 24 (+2.3 [−4.4, 8.9] and +6.8 [−1.2, 14.8] letters, respectively). These data are illustrated in Table 2 and Fig. 3, and the differences among countries in the mean VA changes from baseline to months 12 and 24 are illustrated in Fig. 4.

When the mean change in VA data were stratified by baseline VA (<35 letters, 35–69 letters, and ≥ 70 letters), the least gains by month 12 in both the treatment-naïve and previously treated cohorts were observed in patients with a baseline VA of ≥ 70 letters (+2.2 and −4.3 letters, respectively), whereas the greatest gains by month 12 were observed in patients with lower baseline VA (Fig. 5). By month 24, patients with a baseline VA of ≥ 70 letters experienced marked decreases in their VA

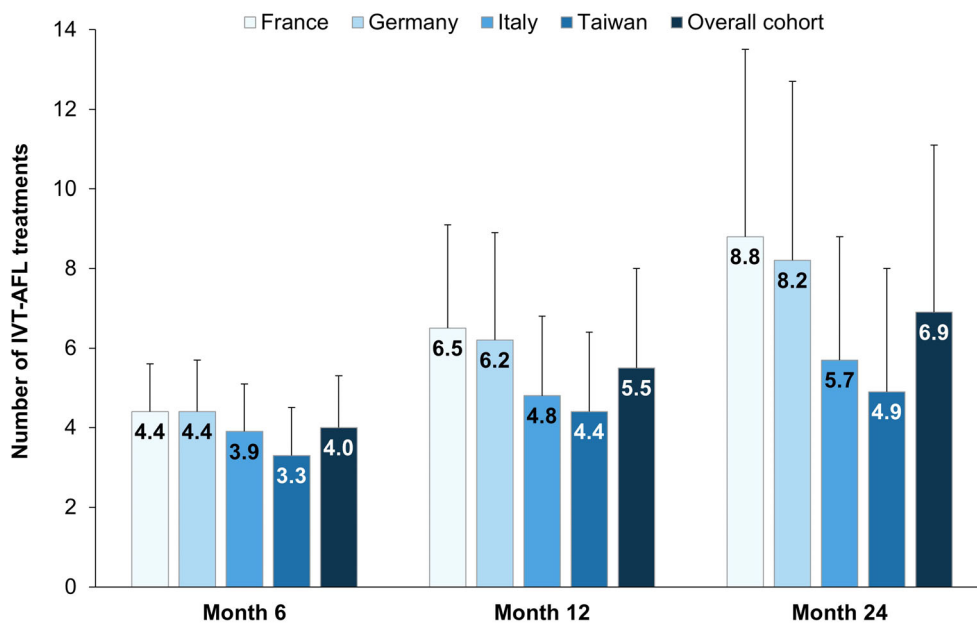


Fig. 7 Mean number of IVT-AFL treatments from baseline to months 6, 12, and 24 in the four countries contributing toward the overall RVO treatment-naïve cohort (France, $n = 138$; Germany, $n = 130$; Italy, $n = 152$; Taiwan, $n = 134$; and overall cohort

$N = 554$). Values are mean \pm SD. Means are calculated across all patients in the FAS. FAS full analysis set, IVT-AFL intravitreal aflibercept, RVO retinal vein occlusion, SD standard deviation

(0.3 and -8.4 letters, respectively), whereas the greatest gains were observed in treatment-naïve patients with a baseline VA of < 35 letters ($+ 26.0$ letters) and previously treated patients with a baseline VA of 35–69 letters ($+ 11.7$ letters).

The proportions of treatment-naïve patients who achieved ≥ 5 -letter, ≥ 10 -letter, and ≥ 15 -letter VA gains by month 24 were 66.5%, 54.9%, and 44.0%, respectively; in previously treated patients, these proportions were 55.7%, 45.9%, and 27.9%, respectively (Figure S1). The proportions of treatment-naïve and previously treated patients who maintained vision over the 24-month study (i.e., lost < 15 letters) were 91.4% and 86.9%, respectively. There were no marked differences between the letter gains and losses by month 12 and month 24, nor between those of the BRVO and CRVO sub-cohorts (data not shown).

In AURIGA, the proportions of patients who achieved ≥ 70 letters by months 12 and 24 were 56.3% (296/526) and 54.3% (287/529) in

treatment-naïve patients, and 45.9% (28/61) and 41.9% (26/62) in previously treated patients. Of patients with a baseline VA of ≥ 70 letters, 82.0% (105/128) of treatment-naïve patients and 52.9% (9/17) of previously treated patients had maintained a VA of ≥ 70 letters by month 24.

Anatomic Outcomes

A rapid decrease in mean CRT was observed in all treatment cohorts (Fig. 6) from a mean baseline of 506 ± 163 and $626 \pm 209 \mu\text{m}$ for the BRVO and CRVO treatment-naïve cohorts and 421 ± 120 and $524 \pm 169 \mu\text{m}$ for the BRVO and CRVO previously treated cohorts. In the CRVO treatment-naïve cohort, the mean change reported by month 6 ($-300 \pm 248 \mu\text{m}$) was maintained through month 12 ($-296 \pm 242 \mu\text{m}$) to month 24 ($-303 \pm 239 \mu\text{m}$). In the BRVO treatment-naïve cohort, a numerically lower but similarly robust decrease in mean CRT was achieved by month 6 ($-216 \pm 176 \mu\text{m}$)

Table 4 NEI VFQ-25 scores at baseline, month 12, and month 24 for the overall RVO treatment-naïve cohort

| Composite score | Overall RVO treatment-naïve (N = 554) |
|----------------------------------|--|
| Baseline | |
| <i>n</i> | 294 |
| <i>Missing</i> | 260 |
| Mean ± SD | 76.3 ± 17.1 |
| Change from baseline to month 12 | |
| <i>n</i> | 104 |
| <i>Missing</i> | 450 |
| Mean ± SD | 6.3 ± 13.8 |
| 95% CI | 3.6, 9.0 |
| Change from baseline to month 24 | |
| <i>n</i> | 62 |
| <i>Missing</i> | 492 |
| Mean ± SD | 4.0 ± 13.6 |
| 95% CI | 0.6, 7.5 |

Too few previously treated patients responded to the questionnaire to allow robust analysis of this cohort
CI confidence interval, *NEI VFQ-25* National Eye Institute Visual Function Questionnaire, *RVO* retinal vein occlusion, *SD* standard deviation

and maintained through month 12 ($-213 \pm 178 \mu\text{m}$) to month 24 ($-208 \pm 187 \mu\text{m}$). In the BRVO and CRVO previously treated cohorts, smaller decreases in mean CRT were achieved and generally maintained over 24 months (month 6, $-139 \pm 139 \mu\text{m}$ and $-232 \pm 168 \mu\text{m}$; month 12, $-122 \pm 131 \mu\text{m}$ and $-214 \pm 182 \mu\text{m}$; and month 24, $-113 \pm 112 \mu\text{m}$ and $-187 \pm 191 \mu\text{m}$, respectively). The mean (95% CI) change in CRT from baseline to month 24 was -247 (-267 , -227) μm for the overall RVO treatment-naïve cohort and -147 (-192 , -102) μm for the overall RVO previously treated cohort; there were no marked differences among countries in these data (data not shown).

The presence of intraretinal fluid (IRF) and subretinal fluid (SRF) over the study period was also assessed in AURIGA. IRF was present at baseline in almost all treatment-naïve and previously treated patients with an SD-OCT assessment at this time point: 95.3% (348/365) and 94.4% (51/54) of patients, respectively (Figure S2). By month 24, this proportion had decreased to 39.9% (75/188) of treatment-naïve patients and 77.8% (14/18) of previously treated patients assessed. In contrast, SRF was present in lower proportions of patients assessed at baseline compared with IRF: 53.2% (190/357) of treatment-naïve patients and 37.7% (20/53) of previously treated patients. By month 24, this proportion had decreased to 5.9% (11/186) of treatment-naïve patients and 16.7% (3/18) of previously treated patients assessed. The persistence of IRF and SRF over time in the two overall RVO cohorts was similar to that observed in the BRVO and CRVO sub-cohorts (data not shown). There were many patients without fluid assessments at each of the key study time points, and there was a trend in increasing missing values toward the end of the study (proportions reported here were calculated based only on the number of patients with assessments).

Treatment Pattern

On average, in both the overall RVO treatment-naïve and previously treated cohorts, the majority of IVT-AFL injections were received within the first 6 months of treatment, with a reduction in injection frequency observed thereafter (Table 3). In the overall RVO treatment-naïve cohort, a mean ± SD of 4.0 ± 1.3 , 5.5 ± 2.5 , and 6.9 ± 4.2 injections were administered by months 6, 12, and 24, respectively, and similarly, in the overall RVO previously treated cohort, 3.8 ± 1.5 , 5.0 ± 2.2 , and 6.3 ± 3.7 injections were administered, respectively. There were no marked differences in injection frequency between the BRVO and CRVO sub-cohorts (data not shown). In the overall RVO treatment-naïve and previously

Table 5 Safety outcomes following intravitreal aflibercept treatment for 24 months

| Safety event, <i>n</i> (%) | BRVO treatment- naïve (<i>n</i> = 327) | CRVO treatment- naïve (<i>n</i> = 228) | Overall RVO treatment- naïve (<i>N</i> = 555) | BRVO previously treated (<i>n</i> = 33) | CRVO previously treated (<i>n</i> = 32) | Overall RVO previously treated (<i>N</i> = 65) | Total (<i>N</i> = 620) |
|--|--|--|---|---|---|--|----------------------------|
| Any TEAE | 78 (23.9) | 68 (29.8) | 146 (26.3) | 1 (3.0) | 6 (18.8) | 7 (10.8) | 153 (24.7) |
| Ocular ^a | 51 (15.6) | 44 (19.3) | 95 (17.1) | 1 (3.0) | 4 (12.5) | 5 (7.7) | 100 (16.1) |
| Any treatment-related TEAE | 4 (1.2) | 6 (2.6) | 10 (1.8) | 0 | 0 | 0 | 10 (1.6) |
| Ocular ^a | 4 (1.2) | 6 (2.6) | 10 (1.8) | 0 | 0 | 0 | 10 (1.6) |
| Most common ocular TEAEs ($\geq 2.0\%$) | | | | | | | |
| Cataract | 7 (2.1) | 6 (2.6) | 13 (2.3) | 0 | 2 (6.3) | 2 (3.1) | 15 (2.4) |
| Conjunctival hemorrhage | 7 (2.1) | 6 (2.6) | 13 (2.3) | 0 | 0 | 0 | 13 (2.1) |
| Dry eye | 9 (2.8) | 3 (1.3) | 12 (2.2) | 0 | 0 | 0 | 12 (1.9) |
| Macular edema | 9 (2.8) | 14 (6.1) | 23 (4.1) | 0 | 0 | 0 | 23 (3.7) |
| Retinal ischemia | 4 (1.2) | 8 (3.5) | 12 (2.2) | 0 | 0 | 0 | 12 (1.9) |
| Visual acuity reduced | 3 (0.9) | 9 (3.9) | 12 (2.2) | 0 | 0 | 0 | 12 (1.9) |
| Discontinuation due to TEAE | 1 (0.3) | 2 (0.9) | 3 (0.5) | 0 | 0 | 0 | 3 (0.5) |
| Discontinuation due to treatment-related TEAE | 1 (0.3) | 0 | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) |
| Any serious TEAE | 18 (5.5) | 22 (9.6) | 40 (7.2) | 0 | 1 (3.1) | 1 (1.5) | 41 (6.6) |
| Ocular ^a | 2 (0.6) | 2 (0.9) | 4 (0.7) | 0 | 0 | 0 | 4 (0.6) |
| All serious ocular TEAEs ^a | | | | | | | |
| Glaucoma | 0 | 1 (0.4) | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) |
| Iris neovascularization | 0 | 1 (0.4) | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) |
| Retinal detachment ^b | 1 (0.3) | 0 | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) |
| Vitreoretinal detachment syndrome ^c | 1 (0.3) | 0 | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) |

BRVO branch RVO, CRVO central RVO, RVO retinal vein occlusion, TEAE treatment-emergent adverse event

^aTEAEs listed under the 'Eye disorders' category in MedDRA

^bThis TEAE was considered a result of the intravitreal injection procedure

^cThe details provided for this case were 'vitromacular traction'

treated cohorts, ≥ 3 consecutive initial monthly IVT-AFL injections at the start of patients' IVT-AFL treatment were received by 54.2% (300/554) and 40.0% (26/65) of patients, respectively.

As shown in Fig. 7, treatment-naïve patients in France received the highest mean number of injections by months 6, 12, and 24 (4.4 ± 1.2 , 6.5 ± 2.6 , and 8.8 ± 4.7), followed by Germany (4.4 ± 1.3 , 6.2 ± 2.7 , and 8.2 ± 4.5), Italy (3.9 ± 1.2 , 4.8 ± 2.0 , and 5.7 ± 3.1), and Taiwan (3.3 ± 1.2 , 4.4 ± 2.2 , and 4.9 ± 2.7).

VA outcomes at month 12 and month 24 stratified based on treatment frequency during the first year indicated that patients who received the highest number of injections had the greatest gains in the treatment-naïve cohort but the least gains in the previously treated cohort (Figure S3).

In the overall RVO treatment-naïve and previously treated cohorts, the last completed treatment interval at month 12 was ≥ 12 weeks in 34.9% (187/536) and 39.3% (24/61) of patients, respectively. At month 24, these proportions increased slightly to 41.0% (220/536) and 41.0% (25/61), respectively.

The mean \pm SD time in the study (i.e., mean time between baseline and the end of observation visit) was 19.9 ± 6.4 months in the overall RVO treatment-naïve cohort and 18.8 ± 6.2 months in the overall RVO previously treated cohort, with 57.2% (317/554) and 69.2% (45/65) of these patients reaching the regular end of observation, respectively. The main reasons for end of observation before study closure in the overall RVO treatment-naïve and previously treated cohorts were loss to follow-up (20.6% [114/554] and 10.8% [7/65]) and switch to another therapy (7.4% [41/554] and 9.2% [6/65]), respectively. There were no marked differences in these outcomes among countries (data not shown).

Figure S4 indicates the mean \pm SD number of visits of each of the three main visit types by months 6, 12, and 24. In general, the number of injection-only visits was slightly higher than the number of monitoring-only visits across all cohorts and time points, with only a few visits being combined (i.e., injection plus

monitoring), suggesting that the treatment regimen followed was mostly pro re nata [26].

Impact of COVID-19

Here, we report data for the treatment-naïve patients, given the possible impact the pandemic may have had on patients' first year of treatment. The mean \pm SD number of injections received by treatment-naïve patients by month 24 was not markedly different between the "pre-COVID" ($n = 330$) and "during COVID" ($n = 224$) groups (7.6 ± 4.5 and 5.8 ± 3.4 , respectively), and this was associated with similar changes in VA and CRT in these two groups. From a mean baseline VA of 52.3 ± 21.7 letters and 49.0 ± 22.1 letters in the "pre-COVID" group and "during COVID" group, respectively, the mean change by month 24 was 11.4 letters in both groups (95% CI [9.0, 13.8] and [8.2, 14.6] letters, respectively). From a mean baseline CRT of $561 \pm 185 \mu\text{m}$ and $545 \pm 202 \mu\text{m}$, the mean (95% CI) change by month 24 was -255 ($-279, -230$) μm and -236 ($-270, -203$) μm in the "pre-COVID" group and "during COVID" group, respectively. These improvements in VA and CRT by month 24 were similar to those achieved by month 12 in the two groups, with improvements in the first year maintained until the end of study (data not shown).

Patient-Reported Outcomes

Vision-related quality of life and other patient-reported outcomes were assessed in AURIGA using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) [27], Hospital Anxiety and Depression Scale (HADS) [28], and Falls Efficacy Scale International (FES-I) [29]. Additionally, resource use and indirect costs were assessed using the Costs and Outcomes of Retinal Disease (COMETA) questionnaire developed by Bayer AG (Appendix II). In the treatment-naïve cohort, there was a clinically relevant improvement (i.e., ≥ 4 -point change) [30, 31] of 6.3 ± 13.8 points (95% CI: 3.6, 9.0) from baseline ($n = 294$) to month 12 ($n = 104$) in the patients' vision-related quality of life

based on the NEI VFQ-25; by month 24 ($n = 62$), patients had maintained a clinically relevant improvement in this outcome versus baseline (4.0 ± 13.6 ; 95% CI: 0.6, 7.5; Table 4); too few previously treated patients completed the NEI VFQ-25 questionnaire to enable analysis of this cohort. No clinically relevant changes were observed between baseline and month 12 with HADS or FES-I, nor did the COMETA questionnaire report any marked changes in healthcare resource use from baseline to month 12 (data not shown). It must be noted that many patients did not complete the voluntary questionnaires at each of the key study time points, and there was a trend in increasing missing values toward the end of the study that did not allow the completion of some of the analyses.

Safety

In the overall RVO treatment-naïve and previously treated cohorts, 26.3% (146/555) and 10.8% (7/65) of patients, respectively, experienced TEAEs (Table 5), with ocular TEAEs occurring in 17.1% (95/555) and 7.7% (5/65) of patients, respectively. Across all patients, the most common ocular TEAE was macular edema (3.7% [23/620]), followed by cataract (2.4% [15/620]) and conjunctival hemorrhage (2.1% [13/620]).

Serious TEAEs occurred in 7.2% (40/555) and 1.5% (1/65) of patients in the overall RVO treatment-naïve and previously treated cohorts (Table 5), whereas serious ocular TEAEs occurred in 0.6% (4/620) of all patients. There was one case of eye infection in a patient with treatment-naïve CRVO; however, this case was not considered serious or treatment-related.

No other cases of intraocular inflammation, including endophthalmitis, were reported, nor were there any cases of retinal vasculitis; one case of retinal neovascularization was observed. The proportion of patients with arteriothrombotic events such as stroke, transient ischemic attack, myocardial infarction, and vascular death was no higher than that expected in control (sham-treated) patients (data not shown) [32].

Three deaths were reported among patients with RVO during the study. In the CRVO treatment-naïve cohort, one sudden death was reported, and another patient experienced a fall with multiple injuries that proved fatal. In the CRVO previously treated cohort, one patient died from cerebral ischemia.

All TEAEs considered to be treatment-related were ocular and were reported in treatment-naïve patients only (1.8% [10/555]); none of these TEAEs were considered serious. The treatment-related TEAEs were conjunctival hemorrhage ($n = 4$), epiretinal membrane ($n = 1$), eye irritation ($n = 3$), eyelid pain ($n = 1$), foreign body sensation in eyes ($n = 1$), macular edema ($n = 1$), ocular hyperemia ($n = 1$), retinal hemorrhage ($n = 1$), visual impairment ($n = 1$), vitreous detachment ($n = 1$), and intra-ocular injection complication (air bubbles in the vitreous; $n = 1$).

Three patients discontinued the study due to TEAEs (CRVO treatment-naïve, $n = 2$; BRVO treatment-naïve, $n = 1$). In the two CRVO treatment-naïve patients, these TEAEs were myocardial ischemia, chest injury, rib fracture, and chest wall hematoma ($n = 1$ each); all four TEAEs were considered serious, with the latter three TEAEs occurring in the same patient. In the one BRVO treatment-naïve patient who discontinued, the TEAEs reported were considered treatment-related but not serious (macular edema and retinal hemorrhage).

For 13.0% (72/554) treatment-naïve patients and 12.3% (8/65) previously treated patients, the attending physician considered concomitant surgery/laser treatment necessary as rescue treatment, whereas in 3.8% (21/554) treatment-naïve patients and 1.5% (1/65) previously treated patients, these procedures were used to treat an adverse event.

DISCUSSION

The AURIGA study was conducted in 11 countries over 24 months to assess long-term effectiveness and safety outcomes with IVT-AFL in patients with DME or macular edema secondary to RVO and to evaluate treatment patterns in routine clinical practice. Here, we report the

results from the AURIGA RVO cohort, which includes patients from France, Germany, Italy, and Taiwan. Overall, the 24-month analysis of the AURIGA study demonstrated that IVT-AFL is effective in the treatment of macular edema secondary to RVO in routine clinical practice, with patients achieving robust improvements in VA and CRT.

By month 12, the mean change in VA was + 13.9 letters in the treatment-naïve BRVO cohort after a mean of 5.2 injections. At month 24, this VA gain was maintained at + 13.2 letters following a mean of 6.5 injections. In the treatment-naïve CRVO cohort, the mean change in VA by month 12 was + 10.5 letters after a mean of 5.8 injections, with a slight decrease reported by month 24 (+ 8.8 letters) after a mean of 7.4 injections. In treatment-naïve patients, those who received more frequent treatment within the first year reported the highest VA gains by month 12, and the inverse was also observed; however, these results are associations and causation cannot definitively be inferred. The reductions in CRT observed in both cohorts by month 12 were maintained by month 24, with a mean change of – 208 μm and – 303 μm (from a baseline of 506 μm and 626 μm) attained by the end of the study in patients with treatment-naïve BRVO and CRVO, respectively.

Even with the lower treatment frequency in AURIGA, the functional and anatomic improvements achieved in the treatment-naïve BRVO cohort by months 12 and 24 are comparable to the results observed after a year in VIBRANT, the key RCT for IVT-AFL in RVO. In the VIBRANT study, patients gained + 17.1 letters by week 52 after a mean of 9.0 injections, and the mean CRT decreased by 284 μm [20].

Treatment-naïve patients with CRVO also obtained clinically relevant improvements in VA and CRT in AURIGA. As expected based on previous RWE [33], these improvements were not as marked as those reported in key RCTs. In the integrated analysis of the GALILEO and COPERNICUS trials, patients with CRVO gained + 16.5 letters by week 52 after a mean of 5.8 (between baseline and week 24) plus 2.6 (between week 24 and week 52) IVT-AFL injections, and the mean CRT was reduced by

418 μm [12]. In more recent RCTs, similar VA gains have been reported: in CENTERA, patients gained + 19.9 letters by week 52 after a mean of 5.3 (between baseline and week 24) plus 3.9 (between week 24 and week 52) IVT-AFL injections [34], whereas in LEAVO, patients gained + 15.1 letters by week 100 after 10.0 injections [35]. As anticipated, lower gains in VA were observed in patients with CRVO compared with BRVO, as the former is associated with more severe vision loss [2, 3].

In AURIGA, previously treated patients with CRVO reported greater VA gains by month 12 than those with previously treated BRVO (+ 10.3 vs. + 5.8 letters; from a baseline of 46.0 vs. 57.2 letters), following a similar mean number of injections (5.1 vs. 5.0). This may be expected, given that lower baseline VA is generally associated with greater gains following treatment [36]; however, CRVO is typically associated with more severe vision loss than BRVO [2–4]. The gains achieved after the first year in these two cohorts reverted to month 6 levels by the end of the study (+ 6.8 vs. + 2.3 letters). As was observed in the treatment-naïve cohorts, previously treated patients with CRVO had a thicker CRT at baseline than those with BRVO (524 vs. 421 μm) and attained a greater reduction in CRT by month 24 (187 vs. 113 μm). The small size of the previously treated cohorts needs, however, to be acknowledged.

Only 54.2% and 40.0% of patients in the overall RVO treatment-naïve and previously treated cohorts received ≥ 3 consecutive initial monthly injections, as recommended on the product label [8, 9]. After month 6 in AURIGA, the treatment frequency decreased in all cohorts, and notably fewer injections were administered on average in the first year than recommended. However, the rapid and robust visual and anatomic improvements gained during the first 6 months were generally maintained over the 24-month study, suggesting that long-term durability can be achieved with IVT-AFL in patients with BRVO and CRVO. Nevertheless, even greater VA gains may have been achieved in these patients with more frequent IVT-AFL treatment, especially within the first year. Notably, the COVID-19 pandemic had minimal impact on key functional and

anatomic endpoints when comparing treatment-naïve patients who began treatment before or during the pandemic.

In the overall treatment-naïve and previously treated RVO cohorts, 42.8% and 30.8% of patients discontinued the study before study closure; loss to follow-up was the main reason for discontinuation. High rates of study discontinuation are a prevailing challenge when evaluating long-term real-world data, and the rates observed in AURIGA are consistent with (and in some cases, lower than) previous observational studies of anti-VEGF therapies in the treatment of RVO [37–39].

While acknowledging the low proportion of responses to the PRO questionnaires in AURIGA, such data can potentially provide key RWE and should be an avenue for further exploration.

The safety profile of IVT-AFL was consistent with previous studies [15, 18, 20, 34, 35]. One case of eye infection was reported; there were no other cases of intraocular inflammation, including endophthalmitis, nor were there any cases of retinal vasculitis. Retinal neovascularization occurred in one patient.

The multiple strengths of the AURIGA study include the prospective design, the long-term study duration, the large number of patients enrolled, and the large number of centers participating across different countries. These factors enabled robust data collection from a heterogeneous group of patients across a variety of real-world settings.

There is a growing demand for RWE in the treatment of retinal diseases, as it provides valuable information that RCTs are not designed to assess [21–23]. Besides being of value to patients and healthcare providers, regulatory bodies, such as the US Food and Drug Administration (FDA), are increasingly making use of RWE in conjunction with data from RCTs to inform decision-making. Many countries have now developed or adopted RWE frameworks, policies, and guidance specifically on the collection and use of observational data [23]. Ensuring the transparency of RWE study design, conduct, and data collection will facilitate decision-making based on such evidence and further develop its value and applications.

The limitations of AURIGA are implicit within the observational nature of the study and its aim to evaluate real-world effectiveness and treatment patterns. Unlike within the setting of a controlled clinical trial, treatment and monitoring schedules in routine clinical practice can be highly variable, as these are at the discretion of the attending physician, and based on their clinical experience in managing the care of patients with RVO. Not all parameters are assessed at each visit, and not all patients attend each of the visits at key study time points. This results in missing data that may limit the interpretation of study endpoints. In AURIGA, this was particularly the case for the previously treated cohort, which was relatively small, and for specific analyses (e.g., fluid persistence and patient-reported outcomes). Of note, fewer countries committed to enrolling previously treated than treatment-naïve patients, and the exclusion criteria of the study reduced the eligible patient population who could be enrolled in the previously treated cohort (i.e., patients could only have been enrolled in this cohort if they had received prior treatment with steroids or intravitreal anti-VEGF agents other than IVT-AFL). Thus, the pre-treated cohort is smaller than the treatment-naïve cohort.

Methodologic limitations of this study are an inherent result of AURIGA being conducted across multiple sites and countries in real-world settings. A variety of charts were used to assess VA, and different modalities and instruments were used to assess anatomic outcomes such as CRT. Conversion between different VA units and the use of different instruments for anatomic evaluations can introduce error and information bias [40–42].

CONCLUSIONS

AURIGA is the largest real-world study to date in patients with macular edema secondary to RVO treated with IVT-AFL. The 24-month analysis of AURIGA demonstrated the long-term effectiveness and safety of IVT-AFL in these patients in routine clinical practice in France, Germany, Italy, and Taiwan. Robust and clinically relevant

improvements were observed in both functional and anatomic outcomes, and these improvements were largely maintained across the duration of the study, even with the relatively low injection frequency after the first 6 months. These findings are promising, as they suggest long-term durability of the effects of IVT-AFL treatment in patients with RVO. Importantly, even greater gains may have been achieved in these patients in routine clinical practice if they had received more frequent injections in line with the product label, particularly within the first year.

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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 1, 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. Audrey Giocanti-Aurégan has acted as a clinical investigator for Bayer and received consulting fees from AbbVie, Alcon, Bayer, Novartis, Roche, and Théa. Simone Donati declares that he has no competing interests. Hans Hoerauf has received consulting fees from AbbVie, Alcon, Allergan, Bayer, Heidelberg Engineering, Novartis, Oxurion, and Roche. Helmut Allmeier is an

employee of Bayer Consumer Care AG, Basel, Switzerland. Kay D. Rittenhouse was a former employee of Bayer USA LLC, Whippany, NJ, United States, and is now retired. Tobias Machewitz is an employee of Bayer AG, Berlin, Germany. Chang-Hao Yang has received consulting fees and grants from Allergan, Bayer, and Novartis.

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. Appendix I in the Supplementary Materials lists the local IRB/IEC committee names and approval numbers in all participating countries where relevant under local law. The AURIGA 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 AURIGA 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 (EFPIA), European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP), 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 independent ethics committee or institutional review board before and during the study. All patients provided written informed consent for participation in this study.

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