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ORIGINAL RESEARCH

Multimodal Imaging to Assess Disease Activity and Predict Fluid Resolution in Patients with wAMD Treated with Brolucizumab: The IMAGINE Study

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ABSTRACT

Background: This prospective, open-label, single-arm, multicenter phase IV study (NCT04774926) evaluated early imaging parameters as predictors of long-term fluid resolution and assessed the efficacy and safety of brolucizumab in treatment-naïve patients with wet age-related macular degeneration (wAMD) in a real-world Italian setting.

Patients and methods: A total of 122 patients aged ≥ 50 years with subfoveal macular neovascularization secondary to wAMD were enrolled. All patients were anti-vascular endothelial growth factor (anti-VEGF)- and investigational treatment-naïve. Brolucizumab (6 mg) was administered intravitreally at baseline and weeks 4 and 8, followed by maintenance dosing every 12 weeks (q12w) or 8 weeks, on the basis of disease activity. Imaging modalities included spectral-domain optical coherence tomography (OCT), OCT angiography, fluorescein angiography, and indocyanine green angiography.

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Disease activity was assessed using anatomical and functional parameters.
***Results*:** No significant predictive anatomical biomarkers for fluid-free status were identified. At week 48, 22.5% of patients achieved q12w fluid-free status. Significant reductions in central subfield thickness were observed, with a median change of −143.0 µm ($p<0.0001$). Median best-corrected visual acuity improved by 5.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline ($p<0.0001$). Ocular adverse events were consistent with the known safety profile of brolucizumab.
***Conclusions*:** Brolucizumab demonstrated effectiveness and safety in a real-world wAMD cohort, aligning with findings from randomized trials. Although no predictive biomarkers were identified, results emphasize the role of multimodal imaging in guiding individualized treatment strategies and highlight variability in patient responses.
***Clinicaltrials.gov ID*:** NCT04774926.

Keywords: Age-related macular degeneration; Wet AMD; Brolucizumab; Predictive anatomical biomarkers; Multimodal imaging; Real-world study

Key Summary Points

Why carry out this study?

Wet age-related macular degeneration (wAMD) is a leading cause of vision loss in the elderly and imposes a significant treatment burden owing to the frequency of intravitreal anti-VEGF injections. Despite clinical trial data on brolucizumab, real-world evidence on its efficacy and the utility of early multimodal imaging biomarkers for predicting fluid resolution in treatment-naïve patients with wAMD was lacking.

The study investigated whether early anatomical imaging biomarkers could predict long-term fluid resolution (absence of intraretinal and subretinal fluid) and evaluated the effectiveness and safety of brolucizumab in a real-world Italian cohort.

What was learned from the study?

Although no significant early imaging biomarkers were identified as predictors of fluid-free status, brolucizumab significantly reduced central subfield thickness (median change: −143.0 µm, $p<0.0001$) and improved median best-corrected visual acuity (BCVA) by 5.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 48 ($p<0.0001$).

The study confirmed the real-world effectiveness and safety of brolucizumab, with over half of patients achieving fluid resolution by week 48, but only 22.5% reaching q12w fluid-free status, reflecting variability in treatment response. The inability to identify predictive biomarkers emphasizes the heterogeneity of wAMD and suggests future research should explore advanced analytical tools (e.g., machine learning) to enhance personalized treatment strategies.

INTRODUCTION

Age-related macular degeneration (AMD) is a chronic, progressive retinal disease and a leading cause of visual impairment, particularly

among older individuals [1]. Globally, AMD caused moderate-to-severe vision impairment in 8.41 million people in 2015, with 5.64% of legal irreversible vision loss cases attributed to the disease [2].

Wet AMD (wAMD) involves macular neovascularization (MNV), a pathological angiogenesis where abnormal vessels from the choriocapillaris invade the subretinal or subretinal pigment epithelium (sub-RPE) space (type 1 and 2 lesions). In addition, type 3 MNV lesions, also known as retinal angiomatous proliferation (RAP), originate within the neurosensory retina and may subsequently extend toward the subretinal or sub-RPE space. This process results in fluid accumulation, hemorrhage, pigment epithelial detachments (PEDs), hard exudates, or subretinal fibrosis [3]. These pathological changes result in photoreceptor damage, progressive vision loss, and, if untreated, eventual irreversible vision loss [4].

Advances in multimodal imaging have enabled more precise and reproducible assessments of wAMD pathology [5, 6]. In particular, techniques such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) allow detailed evaluations of MNV activity, fluid dynamics, and retinal structure [3, 7]. In addition, multimodal imaging determines the anatomical location of MNV, which is used to subclassify the vascular component of the disease process (type 1–3) [8].

The main goal for wAMD treatment is to improve or at least maintain visual acuity. Achieving this requires drying the affected retina by inhibiting new blood vessel growth and reducing fluid leakage [9]. Vascular endothelial growth factor (VEGF) is a major contributor to MNV pathogenesis [3]. Accordingly, the use of intravitreal (IVT) pharmacotherapy targeting VEGF has greatly improved visual outcomes and prognosis for patients with wAMD, becoming the standard of care for this condition [9, 10].

Despite the well-established efficacy of anti-VEGF therapies, the need for frequent IVT injections places a significant burden on patients, their caregivers, physicians, and healthcare systems [11, 12]. This treatment burden can impact adherence and disease monitoring, leading to suboptimal disease management. Long-term observational studies have shown that a substantial proportion of patients with wAMD experience significant vision loss over 3–8 years despite initiating anti-VEGF therapy [9, 13]. Moreover, real-world evidence indicates that wAMD is often undertreated, with many patients receiving fewer injections than recommended, leading to poor visual and anatomical outcomes [9, 14, 15]. These findings highlight the pressing need for strategies to optimize wAMD management and address unmet medical demands.

Brolucizumab 6 mg (Beovu®) is a humanized single-chain antibody fragment inhibitor of VEGF-A approved for wAMD treatment. Owing to its lower molecular weight (~26 kDa), brolucizumab enables the administration of 6 mg in a single 50 µL IVT injection, which may prolong its therapeutic effect and enhance retinal tissue penetration. In the randomized, multicenter, double-masked, active-controlled, phase III HAWK and HARRIER trials, brolucizumab demonstrated potent anatomical efficacy and reduced injection frequency compared with aflibercept [16]. These studies highlighted the importance of early OCT-based disease activity assessments (DAAs) in determining optimal follow-up regimens—every 12 weeks (q12w) versus every 8 weeks (q8w)—for long-term therapeutic success [16]. Furthermore, this evidence underscores the importance of defining predictive biomarkers to guide personalized treatment strategies, reduce monitoring burdens, and improve adherence to anti-VEGF therapy [17, 18].

The phase IV IMAGINE study is the first prospective clinical trial to investigate whether early imaging biomarkers from OCTA and spectral domain (SD)-OCT can predict long-term anatomical response and treatment outcomes in patients with wAMD receiving brolucizumab. The study aims to support treatment decisions and reduce patient burden by identifying early predictors of therapeutic efficacy.

PATIENTS AND METHODS

The IMAGINE study was a 1-year, open-label, single-arm, multicenter, phase IV trial conducted in Italy. The study aimed to evaluate

the predictive value of early anatomical parameters measured by multimodal imaging and the impact of brolucizumab on disease activity and patient outcomes. Eligible participants were treatment-naïve patients with wAMD who provided written informed consent and underwent a screening period of up to 2 weeks, followed by a treatment period of up to 48 weeks. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The study protocol (EudraCT no. 2020-002452-20) was reviewed and approved by the IRCCS Ospedale San Raffaele Ethics Committee in December 2020 (approval no. 332/2020). The trial was registered with ClinicalTrials.gov (ClinicalTrials.gov ID NCT04774926).

Study Population

The study included male and female participants aged ≥ 50 years with active subfoveal MNV secondary to wAMD in the study eye, confirmed by multimodal imaging (OCT, fluorescein angiography, and/or indocyanine green (ICG)). Key inclusion criteria included absence of prior anti-VEGF or investigational treatment for wAMD, and best-corrected visual acuity (BCVA) between 24 and 78 ETDRS letters. Main exclusion criteria were ocular conditions that could confound evaluation (e.g., fibrosis, atrophy, retinal detachment), recent ocular surgery, and systemic conditions such as uncontrolled hypertension or recent thromboembolic events. If both eyes met the inclusion criteria, only one eye was treated—preferentially, the eye with worse baseline best-corrected visual acuity (BCVA). The fellow eye, if affected by wAMD, could be treated with an anti-VEGF agent different from brolucizumab, as per standard clinical practice.

Treatment Regimen

Participants received IVT brolucizumab (6 mg) in three monthly loading doses at baseline, week 4, and week 8. Afterward, participants transitioned to a maintenance regimen q12w, with an option to adjust to q8w on the basis of DAAs of visual and/or anatomical outcomes. Disease activity was first assessed at week 16 and then at each subsequent scheduled treatment visit (q12w/q8w). Participants on the q12w regimen could switch to q8w if disease activity was detected, whereas those on q8w with no disease activity for two consecutive visits could be reallocated to q12w.

Study Measures

The predictive value of early anatomical parameters was assessed through multimodal imaging at each visit from baseline to week 16 in q12w fluid-free participants (i.e., participants without intraretinal fluid (IRF) and subretinal fluid (SRF) at week 48 who maintained a stable q12w treatment regimen through week 48, following the loading phase). Patients who discontinued the study prematurely were considered not q12w fluid-free at week 48. The effect of brolucizumab on visual function, retinal structure, and vascular leakage was assessed prior to treatment at each visit. The key evaluations for early anatomical parameters and effect of brolucizumab on visual function were as follows: fluorescein and indocyanine green angiographies were performed at screening and week 48 in both eyes, to enhance diagnostic precision, especially for detecting polypoidal choroidal vasculopathy (PCV) and for classification of the lesion subtype, and were assessed by the investigator for wAMD and independently by a certified central reading center (CRC); spectral-domain OCT (SD-OCT) was conducted at all visits in the study eye and at screening and week 48 in the fellow eye. Parameters included IRF, subretinal hyperreflective material (SRF), sub-RPE fluid, SHRM, ORT, PED volume, central retinal thickness, and external limiting membrane (ELM) integrity; fluid resolution was defined as absence of IRF and SRF. Investigators performed clinical evaluations, with images also independently analyzed by the CRC; OCTA was performed at all visits (study eye) and at screening and week 48 (fellow eye); MNV morphology was qualitatively assessed by flow size (on the basis of decorrelation analysis) and vessel density (vessel area versus total lesion area). CRC performed blinded analyses of all OCTA images. The baseline visit

was considered complete even if OCTA data were missing or invalid; color fundus photography (CFP) was conducted at each visit (study eye) and at screening and week 48 (fellow eye) for safety monitoring. Screening images were reviewed by the CRC; disease activity assessments (DAAs) were based on BCVA changes and imaging findings (SD-OCT, OCTA, CFP), documented in source records and entered into the electronic case report form. Full details on study measures and the timeline schematization are provided in the Supplementary Material (Supplementary Table 1). For instance, the correlations of the biomarkers with prognosis were not among the aims of the study.

Quality of Life and Psychological Assessments

Patient quality of life and anxiety/depression status were evaluated using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and Hospital Anxiety and Depression Scale (HADS) questionnaires at baseline and week 48. Participants completed these assessments before clinical evaluations.

Safety Assessments

The number of patients experiencing treatment-emergent adverse events (TEAEs), including ocular TEAEs, was reported and categorized by system organ class and preferred term according to standard MedDRA terminology. Vital signs, intraocular pressure (IOP), and ophthalmic assessments were also recorded.

Statistical Analysis

The study aimed to screen around 300 patients to enroll 263 eligible participants. Analysis populations included all screened, enrolled, and dosed patients, as well as those completing baseline assessments. The primary endpoint was tested using a two-sided alpha of 0.05 without adjustment for multiple comparisons. Continuous and categorical data were summarized descriptively, and changes from baseline were assessed using paired *t*-tests or Wilcoxon signed-rank tests, depending on data distribution. Missing data were handled using the last observation carried forward method, with observed data analyzed separately for sensitivity. All analyses were performed using SAS® version 9.4 or later.

RESULTS

A total of 132 patients were screened. Among these, 122 patients (92.42%) were deemed eligible at both the screening and baseline visits and were enrolled in the study. The remaining ten patients (7.58%) discontinued the screening phase because of screen failure (nine patients) or withdrawal of consent (one patient). Of the 122 enrolled patients, 91 (74.59%) completed the study treatment. The primary reasons for treatment discontinuation included adverse events (AEs) in 15 patients (48.39%), decisions by the investigator (6 patients, 19.35%), resignation of the original principal investigator (4

Table 1 Demographic characteristics of patients

Characteristics	Total ($N = 120$)
Age (years)	
Mean (SD)	76.1 (7.94)
Median	77.0
*Q*1–*Q*3	71.5–82.0
Min–max	53–91
Sex, *n* (%)	
Male	50 (41.67)
Female	70 (58.33)
Ethnicity, *n* (%)	
Hispanic or Latino	7 (5.83)
Not Hispanic or Latino	102 (85.00)
Not reported	11 (9.17)
Race, *n* (%)	
White	120 (100.00)

Percentages were computed on safety population

Q1 1st quartile, *Q3* 3rd quartile, *SD* standard deviation

patients, 12.90%), loss to follow-up (3 patients, 9.68%), and withdrawal of consent (3 patients, 9.68%). At the study's conclusion, 97 patients (79.51%) remained in the study. Discontinuation reasons were similar to those for treatment withdrawal.

Patients' Description

Among the 122 enrolled patients, 120 (98.36%) completed the baseline visit and were included in the full analysis set (FAS) and the safety set. The demographics of these patients are presented in Table 1.

Overall, 62 patients (51.67%) were treated in the right eye, and 19 patients (15.83%) had bilateral wAMD at baseline. The most frequent type of predominant MNV lesion was type I (77 patients, 64.17%), followed by type II (25 patients, 20.83%) and type III (8 patients, 6.67%).

Predictive Values of Early Anatomical Parameters

Overall, 27 patients (22.50%) achieved q12w fluid-free status at week 48. A descriptive summary of predictive factors between baseline and week 16 according to q12w fluid-free versus not q12w fluid-free status at week 48 is presented in Table 2. According to the results from univariate logistic models, no factors were statistically significant predictors of q12w fluid-free status (data not shown).

Treatment Regimen

By week 16, 110 patients (91.67%) remained on treatment and were evaluable for treatment regimen assignment. A q12w regimen was assigned to 68 patients (61.82%), while the remaining 42 patients (38.18%) were assigned to a q8w regimen. Investigators who considered hemorrhage on CFP as an indicator of disease activity were significantly more likely to assign patients to the q12w regimen rather than q8w (odds ratio (OR) = 6.49 (95% CI 1.33–31.57), $p = 0.0205$). Similarly, investigators who considered other parameters to assess disease activity had a significantly higher probability of assigning patients to the q12w regimen than q8w (OR = 18.82 (95% CI 1.17–301.51), $p = 0.0381$).

Among patients assigned to the q12w regimen, 39 (35.45%) maintained the treatment regimen until study completion, while 71 patients (64.55%) were assigned to the q8w regimen or switched between the q12w and q8w regimen during the study.

The mean number of IVT injections administered to each patient was 6.3 ± 1.54 (range: 1–8). Most patients received at least six injections: 42 patients (35.00%) received six injections, 33 (27.50%) received seven injections, and 25 (20.83%) received eight injections.

Effectiveness Results

Among the 119 patients (99.17%) with fluid present at baseline, 64 (56.64%) achieved fluid resolution by week 16. By week 48, this proportion slightly decreased to 49 patients (53.26%) (Fig. 1).

OCTA and SD-OCT Assessments

Significant decreases in MNV lesion area were observed. At week 16, the mean change from baseline was –0.476 ± 1.0012 mm^2 ($p = 0.0205$). At week 48, the mean change from baseline was –0.533 ± 0.9053 mm^2 ($p = 0.0073$).

Changes in lesion diameter were significant until week 12, with a mean change from baseline of –0.311 ± 0.5013 mm at week 12 and a median change from baseline of –0.169 mm (Q1; Q3: –0.502; –0.044 mm) ($p = 0.0017$). At week 16 and week 48, the mean lesion's greatest linear diameter was similar to baseline with a mean change from baseline of –0.211 ± 0.5416 mm ($p = 0.0529$) and –0.147 ± 0.5837 mm ($p = 0.2743$), respectively.

Statistically significant differences from baseline were observed in the proportion of patients with IRF cystoid edema at each post-baseline visit. Among patients with available data, the proportion with IRF cystoid edema significantly

Table 2 Potential predictive factors between baseline and week 16 by patients' classification in q12w fluid-free status at week 48 (safety set)

	q12w fluid-free status at week 48		
	No (*N* = 93)	**Yes (*N* = 27)**	**Odds ratio (95% CI)**
Type of predominant MNV lesion, *n* (%)			
Type I + PCV	61 (70.11)	19 (73.08)	Reference
Type II	21 (24.14)	4 (15.38)	0.61 (0.19–2.00)
Type III	5 (5.75)	3 (11.54)	1.93 (0.42–8.82)
Missing	6 (6.45)	1 (1.08)	–
Subretinal pigment epithelium fluid, *n* (%)			
Stable absent	39 (41.94)	12 (44.44)	Reference
Stable present	32 (34.41)	7 (25.93)	0.73 (0.26–2.04)
Improved	20 (21.51)	8 (29.63)	1.31 (0.46–3.69)
Worsened	2 (2.15)	0	0.63 (0.01–27.52)
Subretinal hyperreflective material, *n* (%)			
Stable absent	41 (44.09)	11 (40.74)	Reference
Stable present	33 (35.48)	7 (25.93)	0.79 (0.28–2.27)
Improved	7 (7.53)	4 (14.81)	2.13 (0.53–8.61)
Worsened	12 (12.90)	5 (18.52)	1.55 (0.45–5.35)
Outer retinal tubulation, *n* (%)			
Stable absent	84 (90.32)	25 (92.59)	Reference
Stable present	1 (1.08)	2 (7.41)	5.52 (0.51–59.61)
Improved	3 (3.23)	0	0.47 (0.02–14.92)
Worsened	5 (5.75)	0	0.30 (0.01–7.41)
ELM integrity loss in center 1 mm, *n* (%)			
Stable absent	25 (26.88)	8 (29.63)	Reference
Stable present	43 (46.24)	13 (48.15)	0.94 (0.34–2.59)
Improved	11 (11.83)	3 (11.11)	0.85 (0.19–3.84)
Worsened	14 (15.05)	3 (11.11)	0.67 (0.15–2.94)
Type of PED, *n* (%)			
Stable fibrovascular only	38 (40.86)	13 (48.15)	Reference
Stable not only fibrovascular	28 (30.11)	7 (25.93)	0.75 (0.27–2.10)
From not only fibrovascular to fibrovascular only	24 (25.81)	7 (25.93)	0.87 (0.31–2.47)
From fibrovascular only to not only fibrovascular	3 (3.23)	0	0.41 (0.01–13.21)

Table 2 continued

	q12w fluid-free status at week 48		
	No (*N* = 93)	**Yes (*N* = 27)**	**Odds ratio (95% CI)**
Percentage changes in CST			
n	92	27	NA
Mean (SD)	−31.7 (18.28)	−36.4 (16.85)	NA
Median	−31.7	−35.0	NA
*Q*1–*Q*3	−46.6 to −18.8	−44.0 to −24.7	NA
Min–max	−76 to 16	−73 to −3	NA

Percentages were computed for safety population within "no" and "yes" groups according to q12w fluid-free status

Of note, the category "stable absent" was also considered for cases where the baseline and last measurement collected were "no" even if at least one "yes" was present in one of the other collected measurements. Similarly, the category "stable present" was also considered for cases where the baseline and last measurement collected were "yes" even if at least one "no" was present in one of the other collected measurements. The same was done for the type of PED classification

Intraretinal fluid cystoid edema was not considered as a predictive factor because the presence of IRF was part of the definition of the fluid-free response (absence of IRF and subretinal fluid, assessed by SD-OCT, at week 48 in patients who maintained a stable q12w treatment regimen up to week 48 after the loading phase)

MNV choroidal neovascularization, *CST* central subfield thickness, *ELM* external limiting membrane, *PED* pigment epithelial detachment, *Q1* 1st quartile, *Q3* 3rd quartile, *SD* standard deviation, *95% CI* 95% confidence interval

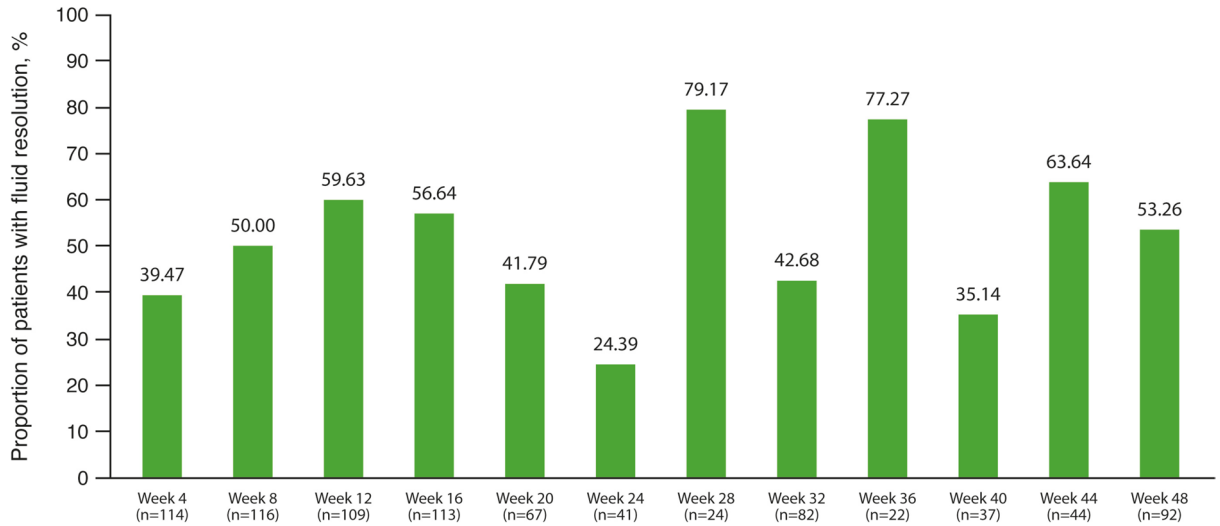

Fig. 1 Bar chart of the proportion of patients with fluid resolution at each visit (safety set—patients with fluid present at baseline)

decreased at week 16 (26.32% versus 56.14%, $p < 0.0001$) and week 48 (23.91% versus 55.43%, $p < 0.0001$). Similarly, significant reductions in the proportion of patients with SRF were observed at all post-baseline visits, except week 40 (where the McNemar test could not be applied). Among patients with available data, the proportion with SRF significantly decreased

at week 16 (28.07% versus 92.98%, $p<0.001$) and week 48 (31.52% versus 93.48%, $p<0.0001$).

Sub-RPE fluid also showed significant reductions from baseline at all post-baseline visits starting at week 8. Among patients with available data, the proportion with sub-RPE fluid significantly decreased at week 16 (34.21% versus 56.14%, $p<0.0001$) and week 48 (32.61% versus 58.70%, $p<0.0001$). Significant changes in the proportion of patients with SHRM were observed only at weeks 4 and 8, with proportions stabilizing from week 12 onward. The proportion of patients with SHRM was 42.11% at baseline, and 46.49% at week 16 ($p=0.3359$). Among the 92 patients with data at both baseline and week 48, the proportion with SHRM was 42.39% at baseline and 35.87% at week 48 ($p=0.2008$).

PED was observed in all patients at baseline and week 16, while it was present in all patients except one at week 48. The most frequent type of PED was "predominantly fibrovascular" (58 patients, 48.33%) at baseline; and "fibrovascular only" at week 16 (78 patients, 68.42%) and at week 48 (67 patients, 72.83%).

No statistically significant differences were detected in the proportions of patients with ORT or ELM integrity loss in the central 1 mm at baseline or any post-baseline visit.

DAAs

Significant anatomical improvements were observed throughout the study. Central subfield thickness (CST) decreased from a mean of 482.6 µm at baseline to 269.5 µm at week 48 (median change: –143.0 µm, $p<0.0001$).

The mean BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) score at baseline was 60.2 ± 15.33 (range 23–90) with a median of 62.0 (Q1; Q3: 53.0; 71.0) and then increased significantly at each post-baseline visit (except week 28) ($p<0.05$). At week 16, the median BCVA score was 69.0 (Q1; Q3: 57.0; 79.0), with a median change from baseline of 4.0 (Q1; Q3: 0.0; 10.0). At week 48, the median BCVA score was 72.5 (Q1; Q3: 57.0; 80.0), with a median change from baseline of 5.5 (Q1; Q3: –0.5; 12.0) ($p<0.0001$).

A spaghetti plot of BCVA ETDRS score grouped by predominant MNV lesion types is shown in

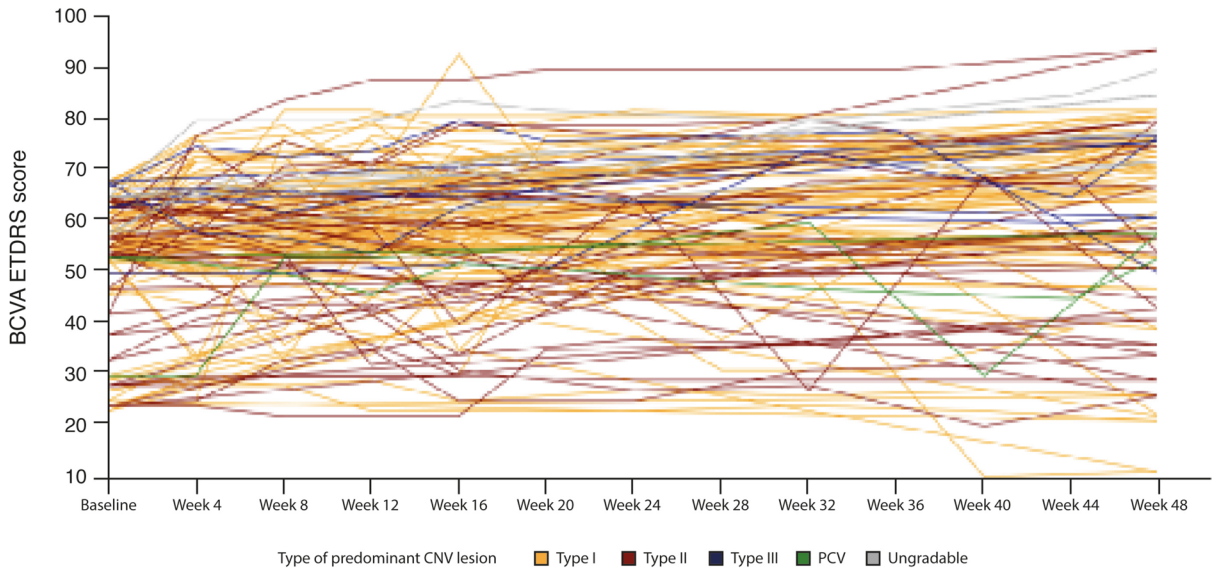

Fig. 2 Changes in best corrected visual acuity (BCVA) scores over time, measured in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, for patients stratified by the type of predominant choroidal neovascularization (MNV) lesion. Individual trajectories are displayed for each patient from baseline to week 48. The MNV lesion subtypes are classified as type I, type II, type III, polypoidal choroidal vasculopathy (PCV), and ungradable lesions

Fig. 2, showing BCVA improvements or declines reflecting treatment outcomes and variations within subgroups.

Quality of Life and Psychological Concerns

The mean change from the baseline in the HADS-A score was –0.78 ± 3.26 (range –12.0–9.0), with a median change of 0.00 (interquartile range (IQR): –2.00–1.00). This change was statistically significant at week 48 (Wilcoxon signed-rank test, $p = 0.0303$). Similarly, the mean change from the baseline in the HADS-D score was –0.10 ± 3.05 (range –16.0–9.0), with a median change of 0.00 (IQR: –1.00–1.00). However, the change in HADS-D score at week 48 was not statistically significant ($p = 0.9076$). Among 120 patients at baseline and 96 patients at week 48 who completed the EQ-5D-5L questionnaire, most reported no difficulty or slight difficulty across all five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at both time points.

Safety and Adverse Events

TEAEs were reported in 58 patients (48.33%) (Supplementary Table 2), with 14 patients (11.67%) experiencing serious TEAEs. Ocular TEAEs were reported in 32 patients (26.67%), with the majority occurring in the study eye (Supplementary Table 3). TEAEs led to treatment discontinuation in 15 patients (12.50%), but no fatal outcomes were reported. No clinically significant changes were observed in vital signs, IOP, or other ophthalmic safety assessments throughout the study.

DISCUSSION

The IMAGINE study assessed early imaging markers for predicting long-term fluid resolution (IRF and SRF absence) in patients with wAMD treated with brolucizumab. While no predictive biomarkers were identified, significant anatomical and functional gains confirmed the drug's effectiveness in real-world settings. The inability to find predictive parameters underscores the difficulty of biomarker discovery in a heterogeneous, non-randomized controlled trial (RCT) population. Contributing factors included limited enrollment (due to coronavirus disease 2019 (COVID-19)), a high rate of ungradable OCTA images, and variability in disease activity assessments. Indeed, unlike the HAWK and HARRIER trials, which employed strict protocols for assessing disease activity [16], this observational study allowed greater flexibility, potentially influencing regimen classifications and predictive analyses.

At the same time, the effectiveness results observed in this study aligned closely with those reported in the HAWK and HARRIER trials, where brolucizumab consistently demonstrated superior anatomical outcomes and noninferior functional outcomes compared with aflibercept [16].

In this study, achieving fluid resolution in over half of the patients (53.26%) at week 48 supports brolucizumab's efficacy in disease stabilization treatment burden reduction. The ability to maintain a q12w regimen in 35.45% of patients further highlights its potential to reduce injection frequency, addressing a key limitation of anti-VEGF therapies in real-world settings [13]. At the same time, the lower proportion of patients maintaining a q12w regimen compared with HAWK and HARRIER (46–56%) may be attributed to the study's observational nature, which allowed investigator discretion in regimen adjustments based on broader criteria than those employed in controlled trials.

The significant reductions in IRF, SRF, and sub-RPE fluid observed at multiple post-baseline visits reflect brolucizumab's robust impact on anatomical disease markers. IRF and SRF are widely regarded as key biomarkers of disease activity in wAMD, as their resolution correlates with improved visual outcomes [9]. The reduction in sub-RPE fluid, which may indicate early pathological changes in wAMD, further underscores the broad-spectrum anatomical efficacy of brolucizumab. These findings align with evidence suggesting that early and sustained fluid control is a key determinant of long-term treatment success in wAMD [15].

The observed CST reduction (median change: −143.0 µm, $p<0.0001$) was comparable to reductions observed in the HAWK and HARRIER trials [16]. This consistency underscores the robust fluid-resolving capability of brolucizumab in reducing retinal thickness across diverse populations and treatment settings.

Similarly, improvements in BCVA reinforce the functional benefits of brolucizumab. A median BCVA change of 5.5 ETDRS letters at week 48, closely mirroring the gains reported in the HAWK and HARRIER trials, highlights the potential of brolucizumab to improve vision in patients with wAMD [16]. These gains are particularly significant given the study's real-world setting, where patient variability, adherence challenges, and heterogeneous baseline characteristics often contribute to suboptimal outcomes compared with clinical trials [9, 15].

The HADS-A score significantly decreased from baseline to week 48, suggesting that anxiety was alleviated after treatment, while other parameters showed improvement but did not reach statistical significance. Recent studies have demonstrated the importance of assessing quality of life parameters, which are influenced by factors such as visual acuity, contrast sensitivity, and age [19, 20]. The lack of statistical significance in these results raises the question of whether more specific scales for wAMD should be used in future studies to assess quality of life parameters with greater sensitivity. In addition, it suggests that other influencing factors should be considered to fully appreciate the impact of changes in a clinical setting.

There were no significant concerns regarding the incidence of TEAEs, which were consistent with previous studies and the approved label [16]. However, one suspected unexpected serious adverse reaction/transient ischemic attack was reported. Focusing on the TESAEs related to the study treatment, reported events included ocular AEs (retinal occlusive vasculitis, uveitis) and nonocular AEs (asthenia, cerebellar ischemia, transient ischemic attack). Each case of retinal occlusive vasculitis and uveitis occurred in one patient, but these events have been previously reported in brolucizumab studies [21–23]. All TESAEs were resolved by the final follow-up visit. The obtained results highlight potential areas for further exploration. While hemorrhage detected via CFP showed a significant association with q12w regimen assignment, the clinical relevance of this parameter requires further investigation owing to the limited number of cases and potential confounding factors. Similarly, the lack of significant predictive value for other anatomical parameters suggests the need for more sophisticated analytical approaches, such as machine learning algorithms, to identify subtle patterns in multimodal imaging data that could serve as reliable biomarkers for treatment response.

The study's limitations included the small sample size, a high proportion of ungradable imaging data, and variability in investigator assessments due to the study's observational nature, which introduced inconsistencies in treatment regimen decisions. In addition, the lack of standardized criteria for disease activity limited the generalizability of the findings to broader populations. At the same time, this was the first real-world study supporting efficacy data (BCVA and CST) observed in RCTs, where patients are highly selected. As the results suggest, patients in clinical practice exhibit high variability in their response, emphasizing the need for real-world studies to evaluate increasingly personalized therapy.

CONCLUSIONS

The IMAGINE study, the first real-world investigation in Italy on brolucizumab for wAMD, evaluated early imaging biomarkers as predictors of long-term fluid resolution. While no significant predictors were identified, the study supported brolucizumab's efficacy and safety, in line with results from randomized trials. The findings underscore the need for additional real-world research to support personalized treatment strategies.

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Data Availability. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of Interest. Marco Lupidi serves as Advisory Board member for Abbvie, Apellis, Bayer, Novartis, and Roche. Mariacristina Parravano reports personal fees from Abbvie, Novartis, Bayer, and Roche outside of the submitted work. Francesco Bandello, Stela Vujosevic, Daniela Bacherini, Angelo Maria Minnella, Fabrizio Giansanti, Chiara Ascardi, and Giovanni Staurenghi have no conflicts of interest to declare.

Ethics Approval. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The study protocol (EudraCT no. 2020–002452-20) was reviewed and approved by the IRCCS Ospedale San Raffaele Ethics Committee in December 2020 (approval no. 332/2020). The trial was registered with ClinicalTrials.gov (ClinicalTrials.gov ID NCT04774926).

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