Review Article

Molecular structure, pharmacokinetics and clinical evidence of brolucizumab: a narrative review

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Abstract: Macular neovascularization (MNV) is the hallmark of neovascular age-related macular degeneration (nAMD), one of the leading causes of vision loss in the developed world. The current MNV standard of care including frequent intravitreal anti-vascular endothelial growth factor (VEGF) injections, although has revolutionized favorably the treatment, places a substantial burden on patients, caregivers, and physicians. Brolucizumab is a newly developed single-chain antibody fragment that inhibits activation of VEGF receptor 2 with *in vitro* affinity and potency comparable to commercially-available anti-VEGF agents. Its small molecular weight and its design allow for high solubility and retinal tissue penetration, and improve binding affinity to the target. Also a high clearance rate leading to minimal systemic exposure was observed. Brolucizumab has shown similar gains in visual acuity compared with other anti-VEGF molecules but a higher and earlier resolution of nAMD related fluid, achieving sustained macular dryness with longer mantainance injection interval ranging from 8 to 12 weeks after monthly loading doses. Rare cases of ocular inflammation also including retinal vasculitis and retinal vascular occlusions referred to an immune-mediated reaction posed safety concerns on selected patients and mantainance treatment interval shorter than 8 weeks. The present review summarizes several key points including the molecular structure and pharmacokinetics, the preclinical and clinical evidence of brolucizumab administration evaluating its efficacy, tolerability, and safety, extended dosing regimens and other indications still under clinical investigation.

Keywords: Neovascular age-related macular degeneration (nAMD); anti-vascular endothelial growth factor (anti-VEGF); single-chain antibody fragment; brolucizumab

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries with a prevalence of 8.7%. In particular, early and advanced stages of AMD reported a prevalence of 8.0% and 0.4%, respectively (1,2). It is assumed that about 10% of the population over 65 years and 25% over 75 years have been diagnosed with AMD (3,4). The worldwide number of individuals with AMD is expected to increase, reaching 288 million cases by 2040 (1). The global incidences of early and advanced AMD were 1.59% and 0.19%, respectively. Those of European descent had the highest annual incidence of both stages of AMD (5).

The risk factors for AMD are categorized in nonmodificable including increased age, European white ancestry, light iris color and genetic variants, and modifiable including diet, sunlight exposure, alcohol consumption, and smoking (6).

AMD progresses from early to advanced stage. The latter, in turn, has been classified into two sub-types: dry or non-exudative (dry) AMD and wet/neovascular or exudative AMD (nAMD) (7,8).

The lesions of the early stage of dAMD include subretinal pigment epithelium (RPE) deposits called drusen, RPE abnormalities, hyperpigmentation, and atrophy, and choriocapillary damage (7). The advanced stage of dAMD involves degeneration and atrophy of the neuroretina, RPE and the choriocapillaris. The atrophic regions tend to be multi-focal, involving the fovea and often bilateral (7,8). In nAMD, macular neovascularization (MNV) is the hallmark of nAMD (9). The clinical manifestations of nAMD also include subretinal and intraretinal fluid, retinal, subretinal, or sub-RPE hemorrhage, lipid exudates, RPE detachment, and RPE tear (7,8). The MNV may evolve into a 'disciform scar' (7,8). Although only 20% of patients with AMD have MNV, this clinical subtype is more aggressive and causes 90% of low vision cases (10,11).

The pathogenic mechanisms of AMD are related to aging, complement activation, lipid metabolism, vitamin A cycle/metabolism, autophagy/mitophagy, extracellular matrix turnover, choroidal vascular dropout, and oxidant-induced and non-oxidant related cellular damage (12).

Several approaches being investigated to reduce the progression of dry AMD including antioxidative drugs, complement cascade inhibitors, neuroprotective agents, visual cycle inhibitors, gene and cell-based therapies (13).

Vascular endothelial growth factor (VEGF) is a key mediator of intraocular neovascularization (14), and its antagonism has been shown to suppress neovascularization in mouse and nonhuman primate models (15-17). We can act against neovascularization counteracting VEGF from binding to its receptor, VEGF receptor-2 (VEGFR2) (18). Anti-VEGF agents inhibit vessel spread, reduce the leakage from the neovascularization, and sometimes lead to regression of neovessels (15,19).

So, the introduction of anti-VEGF therapy by intravitreal (IVT) injection as the gold-standard treatment of MNV has drastically changed nAMD prognosis.

In 2004, the pegaptanib sodium, an aptamer that binds the $VEGF_{165}$ isoform, was approved as the first anti-VEGF agent by the Food and Drug Administration (FDA) (20).

In 2006, Ranibizumab, an antibody fragment that binds all VEGF-A isoforms, was approved by the FDA after the ANCHOR and MARINA studies (19,21,22).

From 2006 to 2013, two anti-VEGF antibody fusion proteins were approved, aflibercept in the United States, Europe, and elsewhere after the VIEW 1 and 2 studies, and conbercept in China after the PHOENIX study (23).

Additionally, ziv-aflibercept and bevacizumab, two anti-VEGF drugs approved for systemic tumor therapy, are used "off-label" for nAMD (24,25).

In the last years, other several drugs working as VEGF antagonist, designed as single-chain variable fragment (scFv), bispecific monoclonal antibody, and ankyrin repeat proteins, and administered intravitreally were developed or are developing (26), including Faricimab, a new drug that simultaneously inhibits VEGF-A and angiopoietin-2 (27), OPT-302, a new human VEGF receptor-3, which blocks VEGF-C and VEGF-D (28), KSI-301, an anti-VEGF antibody biopolymer conjugate (28), RGX-314, a vector encoding a VEGF inhibiting antibody fragment (28), and the abicipar pegol able to inhibit all isoforms of anti-VEGF-A and found to be similar to aflibercept and greater than ranibizumab and bevacizumab in VEGF-A binding affinity (29-32).

From 2000 to 2010, their use in clinical practice has reduced the incidence of blindness by 50% (33). However, the real-world data from the LUMINOUS study have revealed that patients reach only suboptimal visual outcomes, and the overall visual performance is lower than those expected according to randomized clinical trials results (34). Moreover, repeated monthly intravitreal injections over a long time and regular follow-ups pose a significant burden to the major stakeholders in the healthcare system as patients and physicians (19). Unmet needs in the treatment in nAMD include MNV inactivation (35) with a long duration of therapeutic action and a sustainable safety for the patients.

So, alternative dosing regimens that differ from those in the registered clinical trials [q4-week (q4w) or q8-week (q8w)], including pro re nata (PRN) and treat-and-extend (T&E) were used by physicians to reduce the burden (11).

Recently, brolucizumab (BEOVU®, Alcon Research Ltd., a Novartis Company, Fort Worth, TX), a scFv that inhibits all isoforms of VEGF-A, currently approved for the treatment of patients with nAMD in the US, Japan, Australia, Switzerland, and the European Union, has proven to achieve a disease control with a 12-week dosing interval following the monthly loading doses (36-39), thus potentially reducing the treatment burden.

This article describes the molecular characteristics and clinical profile of brolucizumab as a new anti-VEGF drug in the treatment armamentarium for nAMD; we also summarize the main milestones of brolucizumab from its development to its commercial approval.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aes-21-41).

Molecular structure and pharmacokinetics

To date, brolucizumab, also known as RTH258, is the most clinically advanced humanized scFv (26,39). The scFvs are agents with small molecular size, having variable heavy (VH) and variable light (VL) domain chains joined together by a flexible peptide and lacking the fragment crystallizable (FC) region (40). They are also expressed from a single genetic transcript (32). The molecular structure of an antibody in scFv format gives a high efficacy in binding the target (40).

Among the anti-VEGF agents, Brolucizumab has a lower molecular weight (26 kDa) when compared to aflibercept (97 kDa) and ranibizumab (48 kDa) (41). Its slow molecular weight permits a 12-fold higher molar dosing around than aflibercept and a 22-fold higher than ranibizumab (42,43).

Brolucizumab can be concentrated up to 120 mg/mL, so a clinical dose of 6 mg of drug is administered in a single 50-µL intravitreal injection (42).

Brolucizumab showed significantly better ability to bind all VEGF-A isoforms compared to bevacizumab (44), aflibercept or ranibizumab (45). Brolucizumab showed a faster binding affinity to VEGF receptor 2 (VEGFR2) (range, 42- to 54-fold) with 25- to 50-fold lower concentrations than ranibizumab (45). Brolucizumab binding ratio to VEGF-A is 2:1, reducing to 1:1 when drug concentration decreases, while maintaining a full blockage of VEGF-A.

The design of this drug seems to have improve the ratio between the active component of drug and target with a high binding affinity to the target that usually is related to a high persistence of the therapeutic effect (42,46).

Preclinical testing process of brolucizumab was performed on rabbits and cynomolgus monkeys (41,45,47), as for the others anti-VEGF drugs (48,49).

In both animal models, brolucizumab showed higher exposure in the retina and choroid than ranibizumab (45).

The time to maximum retinal drug concentration ranges from 1 to 6 hours for brolucizumab in cynomolgus monkeys (47), compared with 6 hours for ranibizumab in monkeys (49) and 24 hours for aflibercept in rabbits (48,50).

Brolucizumab has a rapid systemic clearance (5.6± 1.5 h) with a potentially lower risk of systemic effects (41,47). Furthermore, it is cleared from the eye of monkeys with a lower half-life (56.8±7.6 h) (47) than ranibizumab (62 h) (49), and aflibercept (53 h) (51). The clearance of brolucizumab is so fast probably due to the absence of a Fc domain which reduces the molecular size. *In vivo* IVT injection of brolucizumab in monkeys demonstrated only mild ocular inflammation (41).

Unlike full-length antibodies, the scFvs are targeted for degradation and have no cumulative effect even after many injections (52).

Brolucizumab revealed its high efficacy as anti-VEGF drug, but also a low systemic exposure and no toxicity in nonhuman primates (41). Potentially, brolucizumab may be administered less frequently than at monthly intervals, so to reduce treatment burden (41).

Clinical evidence

A summary of study data was reported in *Table 1*.

The SEE study

The 6-month, phase I/II, multicenter, double-masked, randomized, ascending, single-dose, active-controlled, parallel-group SEE study (NCT01304693) assessed the safety and efficacy of brolucizumab *vs.* ranibizumab in treatment-naïve nAMD patients (46). In 4.5- and 6-mg brolucizumab dose groups, the mean change in central subfield thickness (CST) after 1 month revealed the noninferiority of brolucizumab to ranibizumab. Duration of treatment effect, as the time between the initial IVT injection and the follow one, was 75 days for the 6-mg dosage of brolucizumab and 45 days for the 0.5-mg dosage of ranibizumab (P=0.04). Over follow-up, mean gains in best-corrected visual acuity (BCVA) after IVT of brolucizumab 6-mg were consistently greater than those obteined after IVT of ranibizumab 0.5-mg (46). The study suggested the efficacy of brolucizumab on CST and BCVA with a durable response for the dose of 6 mg (46). A dose-dependent effect was observed after IVT injection of brolucizumab (46).

The OWL study

The Phase II OWL study (NCT01849692) compared brolucizumab with ranibizumab in treatment-naïve nAMD patients using microvolume of drug administrated by injections or infusions. The study randomized the patients in two different cohorts (brolucizumab and ranibizumab) with a ratio of 10:3. Ranibizumab was included for masking purposes only. On day 0 of the first stage, in the injection group, the patients randomized to brolucizumab received a microvolume of 1.2 mg/10 µL, while, in the infusion group, the patients received a microvolume of 1.0 mg/8.3 µL over 16 minutes. On day 0 of the second stage, patients in the injection group received 0.6 mg/10 µL

Table 1 Preclinical and clinical studies of brolucizumab

Study (NCT)	Phase	Nonhuman primate model/human participants	Sample size (No. for eachtreatment arm)	Type, number of injections, dosing Intervals	Study period	Primary outcome
Preclinical (30)	Preclinical	Cynomolgus monkeys	Total n=29: brolucizumab IVT 1.0 mg (n=9); brolucizumab IVT 6.0 mg (n=9); brolucizumab IV 2 mg/kg (n=11)	IVT injection, bilaterally; single dose IV injection; single dose	IVT: 21 days; IV: 14 days (48-hr sample collection)	Intraocular and systemic: pharmacokinetics of brolucizumab after IVT or IV injection in nonhuman primates
SEE (NCT01304693) (37)	1/2	Humans with treatment-naïve nAMD	Total n=194: brolucizumab 0.5 mg (n=11); brolucizumab 3.0 mg (n=31); brolucizumab 4.5 mg (n=47); brolucizumab 6.0 mg (n=44); ranibizumab 0.5 mg (n=61)	IVT injection; single dose	6 months	Noninferiority in change from baseline to month 1 in CST with brolucizumab *vs.* ranibizumab
OWL (NCT01849692) (39)	2	Humans with treatment-naïve nAMD	Total n=52: brolucizumab 1.2 mg/10 µL injection (n=10)	IVT injection or infusion; single dose	42 days	Percentage of responders who achieved ≥3 of the following criteria: a ≥4-letter gain in BCVA at day 14 or 28, a ≥80 µm decrease in CST at day 14 or 28
OSPREY (NCT01796964) (40)	2	Humans with treatment-naïve nAMD	Total n=89: brolucizumab 6.0 mg (n=44); aflibercept 2.0 mg (n=45)	IVT injection; 3 monthly loading doses, followed by q8 wk dosing until week 40; q12 wk for all brolucizumab patients until week 56	56 weeks	Noninferiority in change in BCVA from baseline at week 12 with brolucizumab *vs.* aflibercept
HAWK (NCT02307682) (41)	3	Humans with treatment-naïve nAMD	Total n=1,078: brolucizumab 3.0 mg (n=358); brolucizumab 6.0 mg (n=360); aflibercept (n=360)	IVT injection; 3 monthly loading doses, followed by q8 or q12 wk dosing based on DAA (brolucizumab); q8 wk dosing (aflibercept)	2 years	Noninferiority of mean BCVA change from baseline at week 48 with brolucizumab *vs.* aflibercept
HARRIER (NCT02434328) (41)	3	Humans with treatment-naïve nAMD	Total n=739: brolucizumab 6.0 mg (n=370); aflibercept 2.0 mg (n=369)	IVT injection; 3 monthly loading doses, followed by q8 or q12 wk dosing based on DAA (brolucizumab); q8 wk dosing (aflibercept)	2 years	Noninferiority of mean BCVA change from baseline at week 48 with brolucizumab *vs.* aflibercept

BCVA, best-corrected visual acuity; CST, central subfield thickness; DAA, disease activity assessment; IV, intravenous; IVT, intravitreal; nAMD, neovascular age-related macular degeneration.

of brolucizumab while patients in the infusion group received 0.5 mg/8.3 µL of brolucizumab. Patients in both treatment groups randomized to ranibizumab received a 0.5 mg/50 µL at each stage (53,54). The efficacy end point was defined as the percentage of patients underwent brolucizumab who achieved at least three of the following criteria including a ≥4-letter gain in BCVA at day 14 and 28; a ≥80-µm decrease in CST at day 14 and 28 (53,54). An efficacious responder rate in the brolucizumab injection group between 70% and 80%, and of 60% in the brolucizumab infusion cohort were reported.

The study demonstrated that BCVA and CST improved after brolucizumab IVT injection or infusion. A predetermined monthly microvolume could be delivered over 6 months potentially using a pump, thus reducing treatment burden (53,54).

The OSPREY study

The OSPREY (NCT01796964) study was a phase II, randomized, double-masked, multicenter study conducted on treatment-naïve patients comparing the safety and efficacy of brolucizumab respect to aflibercept over a 40-week follow-up (55). The patients with nAMD were randomized 1:1 to brolucizumab 6 mg or aflibercept 2 mg. Both drugs were given with the same frequency q8w until week 40. In the study were defined 3 different treatment periods. In the first period the loading doses were administered at baseline, week 4, and week 8. In the second period, including a matching q8w dosing, the injections were performed at weeks 16, 24, and 32, with corresponding assessments up to week 40. The final cycle was extended in the brolucizumab group to allow for assessment of q12-week (q12w) dosing, with the aflibercept group maintained on q8w dosing to week 56 (55). The study demonstrated the noninferiority of brolucizumab compared to aflibercept regarding visual acuity improvement. At week 40, the BCVA improved of +6.3 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline in the brolucizumab group and +5.8 ETDRS letters in the aflibercept group. The patients underwent brolucizumab injection had more stable CST reductions, more frequent resolution of intraretinal and subretinal fluid, and fewer unplanned treatments than patients underwent aflibercept. In the unmasked 12-week follow-up phase including patients with brolucizumab only, around half of the patients maintained visual acuity without any additional rescue therapy (55).

Brolucizumab was effective in a q8w regimen with regard to BCVA, achieving a greater fluid resolution than aflibercept. A q12w dosing interval seemed to allow an adequate treatment in 50% of patients.

The HAWK and HARRIER trials

The phase III, two 96-week, prospective, double-masked, multicentered studies, HAWK (NCT02307682) and HARRIER (NCT02434328), evaluated the efficacy and safety of brolucizumab versus aflibercept in treatment-naïve patients with nAMD over 2 years (36).

In these trials, all patients were treated with 3 monthly doses of brolucizumab or aflibercept, as loading phase. After that, aflibercept was injected on a fixed q8w interval, while brolucizumab was administered every 12 weeks (q12w), but, if disease activity was revealed, the treatment interval was adjusted to permanent q8w.

In order to identify the patients for whom to modify the treatment regimen after loading phase, the protocol guidance at week 16 provided specific functional and anatomical criteria for CST and intraretinal fluid (IRF) status. The analysis of disease activity was realized at week 16 and at each scheduled q12w treatment visit (weeks 20, 32, and 44 in HAWK study and additional evaluations at weeks 28 and 40 in HARRIER) (36). The results were reported as a q12w/q8w regimen and compared to a q8w dosing of aflibercept (36).

In both studies, the noninferiority of brolucizumab to aflibercept in BCVA change from baseline to week 48 was the main endpoint, while the percentage of patients on a q12w treatment interval at week 48, the changes in BCVA and CST at each follow-up visit, IRF and/or subretinal fluid (SRF) status, and safety were secondary endpoints (36).

The primary endpoint was achieved with a mean gain in visual acuity of +6.6 and +6.8 ETDRS letters (HAWK) and +6.9 and +7.6 ETDRS letters (HARRIER) from baseline with brolucizumab and aflibercept, respectively. These functional improvements were sustained up to week 96 (56). Regarding treatment burden at 48 weeks, 56% (HAWK) and 51% (HARRIER) of the patients receiving brolucizumab were treated every 12 weeks after the loading phase. After brolucizumab less disease activity (after loading phase) at week 16 compared to aflibercept was observed (36).

The major reductions in CST were observed with brolucizumab at week 16 and maintained at week 48 (36) and 96 (56), despite the lower number of injections compared to aflibercept (36). In both studies, fewer patients had IRF,

SRF and sub-RPE fluid in the brolucizumab group versus aflibercept at week 16 and 48 (36).

In both trials, a comparison of results between patients receiving brolucizumab 6 mg and patients receiving placebo showed that brolucizumab was associated with an overall functional improvement of approximately 22 ETDRS letters by week 48 and 28 ETDRS letters by week 96 (57).

These studies demonstrated that a q12w regimen of brolucizumab injection has a long durability of efficacy, mainly including a great drying action, so as to reduce treatment burden.

Limitations of the HAWK and HARRIER studies include lack of stratification by geographic region and lack of adjustment for multiplicity in HARRIER. In addition, generalizability of the results is limited to the treatment-naive population and by the complex study design. Neither HAWK nor HARRIER assessed the comparative injection frequency of brolucizumab versus aflibercept under a pre-specified statistical testing method (58). Because the HAWK and HARRIER studies delivered brolucizumab in a formulation that differed from which intended for commercialization, the FDA recommended collecting clinical data from at least 50 patients originally enrolled in the trials and studying the patients for an additional 6 months while treating them with the brolucizumab 6 mg product intended for commercialization (58).

The MERLIN study

The MERLIN study (CRTH258AUS04), a 2-year multicentre, randomised, double-masked phase IIIa study, included pretreated nAMD patients with persistent retinal fluid and frequent treatment need to assess the safety and efficacy of brolucizumab 6 mg q4w treatment regime compared to aflibercept 2 mg q4w. The efficacy of brolucizumab was evaluated by analyzing the change of BCVA from baseline to week 52 as primary endpoint, and stabilization or improvement in BCVA at week 52 and 104, loss and gain in BCVA from baseline to each follow-up visit, change in macular thickness, presence or absence of fluid (IRF, SRF, sub-RPEF), time to first and sustained dry retina finding as secondary endpoints (59).

On May 2021, Novartis® reported the first interpretable year one results of that study (60). However, due to the safety concerns related to the q4w dosing interval, Novartis® has decided to terminate the MERLIN study and all other ongoing trial protocols was amended to discontinue q4w dosing intervals after the loading phase (60).

Fluid resolution

The presence of IRF on OCT scans is a biomarker of disease activity (19). A post hoc analysis of OSPREY revealed that a greater proportion of eyes treated with brolucizumab (61%) compared to eyes treated with aflibercept (35%) achieved resolution of IRF and SRF at week 40 (55). A greater percentage of patients underwent brolucizumab IVT had two or more consecutive "fluid-free visits" than patients treated with aflibercept at week 40 (75% and 46.6% patients with ≥2 consecutive visits, respectively, and 68.1% and 37.7% with ≥3 consecutive visits, respectively) (61). In HAWK and HARRIER studies, fewer patients receiving brolucizumab had IRF and/or SRF at week 16 and week 48. Similarly, fewer patients underwent brolucizumab had sub-RPE fluid at same follow-ups in both trials (36). In HAWK study, the eyes with IRF/SRF at week 96 were 24% after brolucizumab and 37% after aflibercept, respectively. Indeed in HARRIER study, the presence of IRF/SRF was observed in 24% of eyes treated with brolucizumab and 39% in eyes treated with aflibercept (56). The analysis of the phase II and III trials revealed that brolucizumab had better fluid control than aflibercept, both with identical dosing frequencies (q8w) but also with a lower frequency maintenance regime (q12) (39).

Durability of effect

In the first clinical trial, the median time between consecutive injections was 30 days longer in the brolucizumab 3- and 6-mg arms and fifteen days longer in the 4.5-mg arm compared with ranibizumab (46). The OSPREY trial confirmed the longer durability of effect in patients treated with brolucizumab than those treated with aflibercept receiving unscheduled additional injection ("rescue therapy") up to week 40. Approximately 50% of the eyes treated with brolucizumab had stable BCVA during q12w treatment intervals until week 56 (55). The HAWK and HARRIER trials confirmed the longer durability of effect previously revealed by the phase I/II trials. Over 75% of the eyes underwent brolucizumab completing week 48 on a q12w interval showed no disease activity at week 92. That confirmed the therapeutic validity of a q12w treatment interval (56).

Safety profile

The incidence of adverse events (AEs) after brolucizumab

reported in clinical trials was comparable with other data on the other anti-VEGF agents.

The SEE study suggested that brolucizumab was well tolerated. Local AEs including conjunctival hemorrhage and hyperemia, and eye pain were mild in intensity and resolved within a few days without treatment. There were no reported treatment discontinuations due to AEs (46).

In OWL study no safety concerns were reported (53,54).

In OSPREY study, the most frequently reported ocular AEs after brolucizumab injection (occurring in >10% of treated patients) were conjunctival hemorrhage and vitreous floaters (approximately 11% for each AE) (55).

In HAWK and HARRIER, the AEs were similar for both drugs, brolucizumab and aflibercept (36,56). The overall number of AEs was low in both trials (36,56). The most common ocular AEs in the brolucizumab arms was a mild to moderate intraocular inflammation (IOI) including anterior chamber cells and flare, chorioretinitis, iridocyclitis, iritis, and vitritis, well managed with topical corticosteroids and antibiotics (36). Few cases of retinal artery occlusion were reported in both studies (36).

Post market surveillance of brolucizumab reported some cases of IOI and retinal vasculitis (RV) with and without severe visual loss (62-64).

An independent Safety Review Committee, supported by Novartis®, confirmed signs of (RV) and retinal occlusion (RO), and a related risk of visual loss after brolucizumab injection (65). The incidence of IOI was 4.6%. In eyes with IOI, a moderate visual acuity loss (≥15 ETDRS letters) occurred with an incidence of 0.74%. Of these cases, 5 experienced IOI within 3 months after the first injection (65).

Non-interventional retrospective real-world evidence studies on large US databases, the IRIS Registry® (Study HEORUSV201342) and Komodo Healthcare Map™ (Study HEORUSV201368), were performed in parallel to better understand the incidence of AEs after initiating treatment with brolucizumab for up to 6 months (66,67).

Both US databases had large patient populations (IRIS® n=10.654; Komodo n=11.161). The findings on all forms of IOI (IRIS®, 2.39%; Komodo, 2.40%) and, particularly on RV and RO (IRIS®, 0.55%; Komodo, 0.56%), were consistent between the two databases (66,67).

Patients with IOI and/or RO in the 12 months prior to the first injection of brolucizumab were more likely to present with similar events in the 6 months after a brolucizumab injection than patients with no prior history of aforementioned events. Moreover, both databases revealed that the AEs were observed more frequently after the first injection (50.98%) and their occurrence decreased after the second and third injection. In retrospective studies and clinical trials, a higher risk for IOI including RV and/or RO has been observed in females. A higher incidence was also observed in Japanese patients (66-68).

In a recent update on safety recommendations, Novartis® in agreement with the European Medicines Agency (EMA), communicated the results of BASICHR0049 study. This study, analyzing the blood samples from 5 nAMD patients who developed RV and/or RO after brolucizumab injection and 6 nAMD control patients who had no signs/symptoms of IOI during treatment, revealed a causal link between the treatment-emergent immune reaction against brolucizumab and its related RV and/or RO, usually in presence of IOI. The activation of immune response factors against brolucizumab, including anti-drug antibodies (ADA) and neutralising antibody response, the identification of a T cell response to brolucizumab and *in vitro* stimulation of platelet aggregation in presence of brolucizumab and VEGF-A were searched. In the samples from patients who experienced AEs, the presence of high titre ADAs, with a IgG-driven response against B cell on the brolucizumab and a memory T cell activation revealed a humoral and cellular immune response against brolucizumab 3–5 months after the last injection and occurrence of AEs. In the control group, ADAs, when present, had lower titres (68). So, IOI events including RV and RO can be considered as immune-mediated events.

In the MERLIN study, IOI complicated by RV and RO occurred more frequently after brolucizumab 6 mg treatment with a q4w interval (9.3%) compared to aflibercept 2 mg at the same interval (IOI: 9.3% *vs.* 4.5% of which RV: 0.8% *vs.* 0.0%; RO: 2.0% *vs.* 0.0%.). The overall rate of vision loss (≥15 letters) due to all causes was 4.8% in the brolucizumab group and 1.7% in the aflibercept group. The IOI occurrence was higher also when compared to the brolucizumab 6 mg q8w/q12w interval treatment (4.4%) in the phase III clinical studies. Therefore, the maintenance doses of brolucizumab after the loading phase should not be administered at intervals less than 8 weeks (60).

In the recommendations to healthcare professionals, is reported that the patients should be instructed in how to recognise early signs and symptoms of IOI and to seek medical attention without delay, if these side effects are suspected. In addition, the treatment with brolucizumab should be discontinued and the events should be

promptly managed (68).

Beyond fixed dose regimen

Several phase IIIa and b studies are planned or have already started, aiming at to address exploring efficacy and durability of individualized treatment strategies (69). A randomized, double-masked, multicenter study called TALON (NCT04005352), aimed to demonstrate that brolucizumab allows for longer treatment intervals than aflibercept in a treat-to-control regimen in treatment-naïve nAMD patients, started recruiting in September 2019.

It is known that some patients required more intensive (i.e., monthly) treatments due to the persistence of activity of MNV. Indeed, previous trials have not assessed brolucizumab given with a regimen other than q8w. The MERLIN study was aimed to evaluated the efficacy of monthly brolucizumab compared to monthly aflibercept in pretreated patients with persistent retinal fluid after a switch from active aflibercept treatment (59). However, safety concerns on monthly treatment with brolucizumab were raised after the analysis of first results of MERLIN study (60), as previously mentioned in this paper.

Ongoing clinical trials

The efficacy of brolucizumab is also being evaluated in other pathologies responsive to anti-VEGF agents, such as diabetic macular edema [in the BUZZARD study (NCT04079231) and the noninferiority studies KESTREL (NCT03481634), KITE (NCT03481660), and KINGFISHER (NCT03917472)), and retinal vein occlusion (in the RAPTOR (NCT03802630) and RAVEN (NCT03810313) studies] (39).

KESTREL is a randomized, double-masked, noninferiority study including participants with type 1 or 2 diabetes, BCVA ranging from 20/32 to 20/320 and DME with a CST ≥320 µm. The experimental arms compare 3.0 and 6.0 mg of brolucizumab given at q6w interval for 5 IVT injections followed by a maintenance regime at q8w or q12w until the end of the study. The comparator for noninferiority is 2.0 mg aflibercept given at q4w interval for 5 injections and then at q8w as maintenance until the end of the study. The primary endpoint was the change of BCVA at week 52 compared to baseline; secondary endpoints included the proportion of patients treated with brolucizumab with a maintenance regime of q12w up to week 52, and the CST reduction from baseline. The study reached full enrollment with 571 patients in March 2020 and its completion is expected in 2021 (70,71).

KITE is an international, randomized, noninferiority trial comparing brolucizumab with aflibercept for DME. This study includes treatment-näive patients with diabetes complicated by nonproliferative DR and DME with a CST ≥320 µm. Patients in one study arm will undergo 5 loading IVT injections of 6.0 mg of brolucizumab followed by maintenance therapy. The comparator is 2 mg aflibercept administered for 5 loading doses followed by maintenance therapy. The primary outcome is the change in visual acuity over 52 weeks. KITE has completed enrollment with 361 patients. Recently, the results of KITE study were reported. Brolucizumab 6 mg was non-inferior to aflibercept 2mg in the change of BCVA. More than 50% of patients underwent brolucizumab had a maintenance regime of q12w over 52 weeks. Brolucizumab showed greater reduction in CST over 40 and 52 weeks. Furthermore, brolucizumab demonstrated an overall well-tolerated safety profile that was comparable to aflibercept with an equivalent rate of IOI between the two drugs (70,71).

In the phase III study, KINGFISHER, patients with DME were randomly assigned to one of the treatment arms: 6.0 mg of brolucizumab every 4 weeks or 2 mg of aflibercept every 4 weeks. The primary outcome was the change in BCVA from baseline to 12 months. Data from the full enrollment of 521 patients are expected in 2021 (70,72).

The RAPTOR (73) and RAVEN (74) studies were undertaken to assess safety and efficacy of brolucizumab *vs.* aflibercept in patients with functional impairment due to branch or central retinal vein occlusion related macular edema. Both studies included six initial monthly injections, followed by 48 weeks of individual flexible treatment. The active comparator is injected with the same protocol.

Conclusions

Brolucizumab is a newly developed anti-VEGF molecule for nAMD treatment. Its pharamacokinetic and pharamcodynamic have permitted to reduce the systemic exposition and increase the local exposition to the drug.

It has shown similar gains in visual acuity compared with other anti-VEGF molecules but a higher and earlier resolution of nAMD related fluid. Furthermore, achieving sustained retinal dryness with longer injection intervals revealed a longer durability of effect.

The advantages of brolucizumab are expected to improve long-term outcomes of nAMD patients, reducing treatment

burden and, perhaps, increasing patient adherence and persistence in treatment.

Additional pieces of evidence are needed regarding the clinical safety of brolucizumab and its clinical use in other anti-VEGF indications.

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Footnote

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