[redacted]	**Statistical Analysis Plan**
	Sponsor: Novartis **Protocol: CRTH258AIT04**

CRTH258AIT04 / NCT04774926

One year, single arm, open label, multicenter, phase IV study using multimodal imaging to guide disease activity assessment through innovative early predictive anatomical biomarkers of fluid resolution in wAMD patients treated with brolucizumab – IMAGINE study

Authors	[redacted], Senior Statistician
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Document History

Status and Version	Release Date	Change Description	Reason/Comment
Draft Version 0.1	11-SEP-2023	N.A.	N.A.
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Draft Version 0.3	22-NOV-2023	[redacted] Further details included in section 4.4.1 for partial dates and in section 6.3.2.4 for patients without fluid resolution. Graphical representation of CST values and a description of this parameter on patients with BCVA ETDRS score lower than 69 letters at baseline were included in section 6.3.2.2. Graphical representation of BCVA ETDRS score values was included in section 6.3.2.3 and all analysis on BCVA results repeated on patients with BCVA ETDRS lower than 69 letters at baseline. Details of total number of parameters used to choose the treatment regimen and on all possible combinations were included in section 6.3.2.5 together with additional analysis on SD-OCT parameters at baseline and type of predominant CNV lesion by BCVA or CST groups based on changes at Week 12. Evaluation of anxiety/depression based on treatment was deleted from section 6.3.2.6. Section 1.1 was update accordingly to changes described. Section 6.3.1 was updated to consider as predictor variables that reflect changes	Sponsor's review Internal Review

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Status and Version	Release Date	Change Description	Reason/Comment
		between baseline and week 16 when measured at more than one timepoint.	
Final Version 1.0	28-NOV-2023	First Final Release	Sponsor's approval

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Authorization

The signatures on this page indicate review and approval of the Statistical Analysis Plan, version 1.0, dated 28NOV2023.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AMD	Age-related Macular Degeneration
BCVA	Best-Corrected Visual acuity
CFP	Color Fundus Photography
CNV	Choroidal Neovascularization
COVID-19	Coronavirus Disease 2019
CRC	Central Reading Center
CRT	Central Retinal Thickness
CST	Central Subfield Thickness
DA	Disease Activity
DAA	Disease Activity Assessment
eCRF	Electronic Case Report Form
ELM	External Limiting Membrane
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	EuroQoL five dimensions and five levels
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
HADS	Hospital Anxiety and Depression Scale
ICGA	IndoCyanine Green Angiography
IOI	IntraOcular Inflammation

IOP	IntraOcular Pressure
IRF	IntraRetinal Fluid
IVT	Intravitreal injection
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography
PCV	Polypoidal Choroidal Vasculopathy
PED	Pigment Epithelium Detachment
q8w	every 8 weeks
q12w	every 12 weeks
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SHRM	Subretinal Hyperreflective Material
SmPC	Summary of Product Characteristics
SRF	Subretinal Fluid
sub-RPE	sub-Retinal Pigment Epithelium
UNG/P	Ungradable due to pathology
UNG/Q	Ungradable due to quality
VAS	Visual Analogue Scale

VEGF	Vascular endothelial growth factor
wAMD	wet Age-related Macular Degeneration
WHO	World Health Organization

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1. INTRODUCTION

This statistical analysis plan (SAP) is focused on the planned final analysis for the study CRTH258AIT04 based on the Protocol Version 02, dated November 11, 2021.

1.1. Changes from The Study Protocol

For SD-OCT parameters, in the study protocol, the Volume of Pigment-Epithelium Detachment (PEDs) defined as irregularly elevated lesions produced by the growth of the choroidal neovascular membrane and the accumulation of fluid or material in the sub-RPE space is planned to be evaluated as continuous variable (quantitative parameter). However, it was not possible to measure this volume according to the CRC evaluation. Consequently, the following qualitative parameters will be provided by CRC: the presence of PED will be summarized considering the possible values (i.e., 'No', 'Yes', 'UNG/P', 'UNG/Q') and in case of PED presence, a description of the type of PED will be provided considering the predominant feature as fibrovascular only, predominantly fibrovascular, purely serous, predominantly serous, drusenoid PED, UNG/P, UNG/Q.

Based on the study protocol, the primary endpoint should be analyzed according to Recursive Partitioning and Amalgamation (RECPAM) classification-tree analysis followed by multivariable logistic regression model. The RECPAM procedure was specified to evaluate interactions between imaging measurements assessed by OCT, OCTA, FA, ICGA and CFP and to identify distinct and homogeneous subgroups of participants in terms of q12w fluid-free participants at Week 48. This procedure should also have the aim to select the variables to be included in the multivariable logistic regression model and how to include them (for continuous, a threshold is identified during RECPAM). Based on data analyzed for the planned interim analysis, the image's grading of SD-OCT and mainly OCTA was affected by many ungradable values due to image's quality or due to pathology providing a great number of missing data that in RECPAM procedure cannot be managed. Moreover, the initial planned number of 263 enrolled patients wasn't reached, and the final number of 122 enrolled patient is too small for this type of the analysis. For these reasons, the RECPAM procedure will not be performed and in section 6.3.1 a different method to consider these variables in the in the multivariable logistic regression model and to choose them will be planned and explained. Moreover, the primary outcome will be considered as 'failure' also for patients who discontinued treatment during the study since for these patients the maintenance of a stable q12w regimen assigned at Week 16 up to Week 48 can not be observed and, thus, also these cases, will be considered as intercurrent event.

Moreover, in the primary analysis OCTA assessments planned in the study protocol will not be considered since based on interim analysis, it was observed that for these parameters most values will be missing.

For what concern the LOCF approach reported in the study protocol, this approach will be maintained for the predictors to be included in the analysis of the primary endpoint since the focus is on the first visits (from baseline to Week 16) and all enrolled patients should perform these visits independently of treatment regimen that will be followed by each patient. For the secondary endpoints, LOCF approach will not be applied because after Week 16 each patient will have different scheduled of visits based on treatment regimen. The LOCF approach can be considered only until Week 16 but (1) for OCTA the number of missing data will lead to most data imputed than the one observed, (2) for SD-OCT the approach is applied in the analysis of primary endpoint, (3) for BCVA the LOCF approach will be provided until Week 16, (4) for HAD and EQ-5D-5L questionnaires the LOCF approach will not applied since only two assessments of these questionnaires are planned in the study.

As performed for interim analysis, all analysis will be conducted on Safety population since during the interim analysis, in which all enrolled patients were considered (see section 6.6 for further details), the FAS and Safety populations include the same set of patients since per definitions of the study protocol, the FAS considered all enrolled patients who completed the baseline visit and all of them are treated and consequently all of them belong to Safety population.

The evaluation of prevalence of anxiety and depression will be performed only based oh HAD questionnaire and not based in terms of treatment that patients could have received for anxiety/depression.

The following additional analysis will be included:

- SD-OCT parameters at baseline and type of predominant lesion will be also analyzed according to BCVA groups and CST groups based on changes at Week 12 in patients who performed Week 16 and were still on treatment at this timepoint.
- A graphical representation of BCVA ETDRS score and CST by means of spaghetti plot will be provided.
- Analyses on CST and BCVA will be also performed on patients with BCVA ETDRS score lower than 69 letters at baseline.

[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	VARIABLES	ENDPOINTS
Primary objective(s): The primary objective is to assess the predictive value of early anatomical parameters measured by multimodal imaging from Baseline to Week 16, in brolucizumab-treated participants with wAMD who present fluid resolution (i.e. absence of IRF and SRF) at Week 48 and have maintained the q12w treatment regimen up to Week 48 after the loading phase, defined also as fluid-free response (q12w fluid-free participants), compared with participants under a more frequent regimen and/or not fluid-free at Week 48.	To define the outcome of interest: • Intraretinal fluid (IRF) based on SD-OCT at Week 48 • Subretinal fluid (SRF) based on SD-OCT at Week 48 • Regimen assigned and followed during the study The following variable will be considered as predictive factors: 1. Basal CNV lesion type (i.e., Type of predominant CNV lesion) 2. SD-OCT Parameters at each visit from Baseline to Week 16: • Sub-retinal pigment epithelium (sub-RPE) fluid • Subretinal Hyperreflective Material (SHRM) • Outer Retinal Tubulation (ORT) • ELM integrity loss in center 1 mm • Type of PED • Center Subfield Thickness (CST)	**Primary endpoint(s):** Early predictive factors of fluid-free response, which is defined as the absence of IRF and SRF (assessed by SD-OCT) at Week 48 in patients with a stable q12w treatment regimen up to Week 48 after the loading phase. The variables considered as potential predictive factors in the statistical model will be selected among the following qualitative and quantitative anatomical parameters: 1. Basal CNV lesion type (i.e., Type of predominant CNV lesion), as assessed by SD-OCT at Baseline and FA, ICGA and CFP at Screening 2. Parameters assessed by SD-OCT at each visit from Baseline to Week 16, of which the main are presence/absence of sub-RPE fluid, subretinal hyperreflective material (SHRM), outer retinal tubulation, status of the External Limiting Membrane (ELM) and measurement of central retinal thickness (CRT) and type of PED

OBJECTIVES	VARIABLES	ENDPOINTS
Secondary objective(s): 1. To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wAMD from Baseline to Week 48	1. OCTA qualitative parameters graded by CRC: • Branching vessels • Peripheral Anastomotic Arcades • Vascular Loops • Dark Halo • Presence CNV lesion and its involvement of the foveal center 1. OCTA quantitative parameters graded by CRC: • CNV flow size including Total CNV lesion area (mm^2) and Greatest linear diameter of lesion (mm) • Vessel density of the lesion including CNV vascular density (%)	**Secondary endpoint(s):** 1. Change in OCTA features assessed by qualitative (branching vessels, peripheral anastomotic arcades, vascular loops and dark halo) and quantitative criteria (CNV flow size, and vessel density) from Baseline up to Week 48
2. To evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SD-OCT parameters of wAMD from Baseline to Week 48	2. SD-OCT qualitative parameters graded by CRC: • Intraretinal fluid (IRF) including the subcategories: (1) IRF in center 1 mm and (2) IRF at foveal center. • Subretinal fluid (SRF) including the subcategories (1) SRF in center 1 mm and (2) SRF at foveal center. • Sub-retinal pigment epithelium (sub-RPE) fluid including the subcategory sub-RPE in center 1 mm	2. Change in SD-OCT features assessed by qualitative (IRF, SRF, sub-RPE fluid, status of ELM, SHRM, outer retinal tubulation and presence and type of PED) and quantitative criteria (CRT) from Baseline up to Week 48

OBJECTIVES	VARIABLES	ENDPOINTS
	• Subretinal Hyperreflective Material (SHRM) including the subcategories (1) SHRM in center 1 mm and (2) SHRM at foveal center. • Outer Retinal Tubulation (ORT) including the subcategory ORT in center 1 mm • Status of the ELM as an indicator of retinal integrity considering ELM integrity loss in center 1 mm • Presence and type of PED 2. SD-OCT quantitative parameters graded by CRC: • Center Subfield Thickness (CST)	
3. To evaluate the effect of brolucizumab on the evolution of functional parameters of wAMD from Baseline to Week 48	3. BCVA ETDRS Score	3. Change in BCVA from Baseline up to Week 48
4. To evaluate the effect of brolucizumab on sustained dryness from Baseline to Week 48	4. SD-OCT dates, Intraretinal fluid (IRF) and Subretinal fluid (SRF)	4. Time to reach sustained dryness of the study eye, as defined by the absence of IRF and SRF for at least 2 consecutive visits and for at least 3 consecutive visits 4. Cumulative incidence of sustained dryness of the study eye, i.e. the absence of IRF and SRF for at least 2 consecutive visits and for at least 3 consecutive visits

OBJECTIVES	VARIABLES	ENDPOINTS
5. To evaluate the reasons underlying the Investigators' choice of brolucizumab treatment regimen (q21w or q8w) at Week 16	5. Parameters considered to assess the presence of disease activity: • BCVA • Leakage at FA/ICGA • Central Subfield Thickness (CST) at SD-OCT • Intraretinal fluid (IRF) at SD-OCT • Subretinal fluid (SRF) at SD-OCT • Subretinal pigment epithelium (sub-RPE) fluid at SD-OCT • Retina Pigment Epithelial Detachment volume at SD-OCT • Central Retinal Thickness (CRT) • Subretinal hyperreflective material (SHRM) at SDOCT • CNV size at OCTA • Vessel density at OCTA • Vessel morphology at OCTA • Hemorrhage at CFP • Other	5. Determinants in the Investigator's choice of brolucizumab dosing regimen (q12w or q8w) at Week 16 (i.e. BCVA, IRF, SRF, sub-RPE fluid, presence of hemorrhages, CRT, OCTA anatomical parameters and/or 3-field CFP)
6. To evaluate anxiety/depression in patients with wAMD treated with brolucizumab	6. HADS questionnaire	6. Change in Hospital Anxiety and Depression Scale (HADS) scores from Baseline to Week 48
7. To evaluate quality of life in patients with wAMD treated with brolucizumab	7. EuroQol-5D-5L questionnaire	7. Change in EuroQol-5D-5L (EQ-5D-5L) scores from Baseline to Week 48

OBJECTIVES	VARIABLES	ENDPOINTS
8. To assess the safety and tolerability of brolucizumab	8. Adverse Events	8. Incidence of Ocular and Non-ocular AEs throughout the study

[redacted]

3. BACKGROUND AND RATIONALE

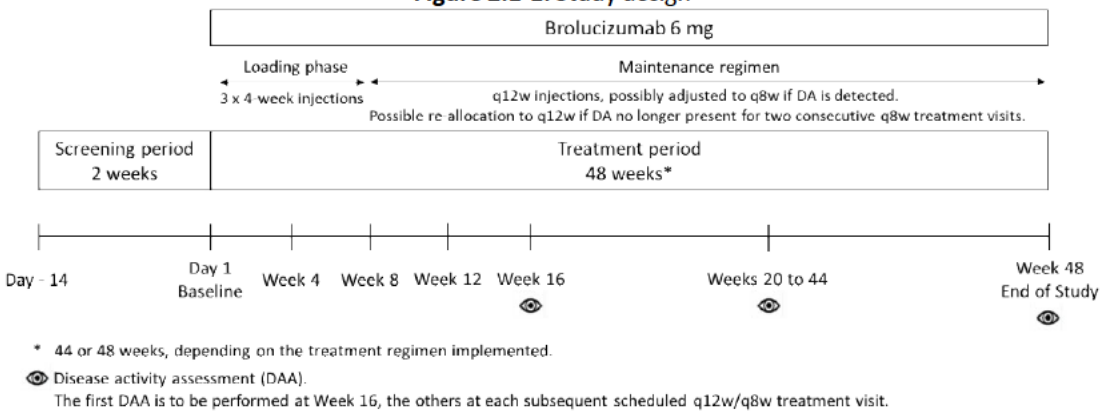
3.1. Overall Study Design and Plan Description

This is a one-year, open-label, single arm, multicenter, phase IV study that will be conducted at approximately 30 centers in Italy.

Patients with untreated active subfoveal Choroidal Neovascularization (CNV) secondary to wAMD who provide signed informed consent and meet all eligibility criteria will be included in the study. Approximately 300 patients are planned to be screened (12% screening failure rate expected) to enroll 263 evaluable participants. Enrolment was closed on October 2022, with 132 screened patients and 122 patients were enrolled. The duration of the study treatment for enrolled patient will be of maximum 48 weeks.

The study consists of a screening period of up to 2 weeks and of a treatment period with brolucizumab from Baseline (Day 1) up to Week 48 (refer to Figure 2.1-1).

Figure 2.1-1: Study design



* 44 or 48 weeks, depending on the treatment regimen implemented.

Disease activity assessment (DAA).
The first DAA is to be performed at Week 16, the others at each subsequent scheduled q12w/q8w treatment visit.

3.2. Selection of Study Population

The study population includes male and female participants aged 50 years or older diagnosed with active subfoveal CNV secondary to wAMD in the study eye, not treated previously with any anti-VEGF drugs or investigational drugs (other than vitamin supplements) for this disease and able to comply with study procedures.

Since the focus of the study is on eyes, if both eyes are eligible as per the inclusion and exclusion criteria described in *Section 5.1 Inclusion Criteria* and *Section 5.2 Exclusion Criteria* of the study protocol only one eye should be treated during the study, the eye with the worse visual acuity (BCVA) at baseline will be selected as the study eye. If both eyes have the same BCVA, it is recommended to select the right eye as the study eye.

A complete list of all inclusion/exclusion criteria is provided in *Sections 5.1 Inclusion criteria* and *5.2 Exclusion criteria* of the study protocol respectively.

3.3. Treatment

3.3.1. Treatment Administered

The investigational drug is brolucizumab 6 mg in solution, administered by means of intravitreal (IVT) injection.

Brolucizumab will be provided in single use, sterile, pre-filled syringes. Each pre-filled syringe contains 19.8 mg brolucizumab in 0.165 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6 mg of brolucizumab.

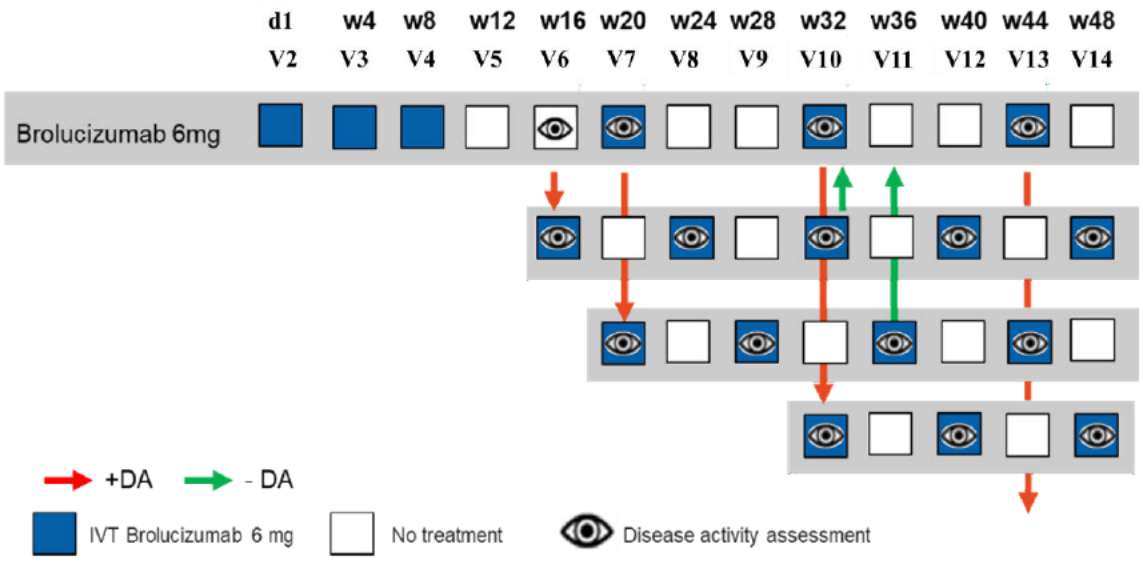
Since the volume contained in the pre-filled syringe (0.165 ml) is greater than the recommended dose (0.05 ml), a portion of the volume contained in the pre-filled syringe must be discarded prior to administration. To expel the air bubble along with excess medicinal product, the plunger should be slowly depressed until the edge below the dome of the rubber stopper is aligned with the 0.05 ml dose mark (equivalent to 50 µl, i.e., 6 mg brolucizumab). Novartis will ensure sufficient supplies of brolucizumab for treatment use to allow for completion of the study.

No study treatment dose adjustment is permitted. Deviations to dose intervals during the initiation phase and/or dose adjustments during the whole study are not allowed. Interruption of study treatment is allowed if warranted by an adverse event.

As per Beovu® SmPC, the recommended dose of 6 mg brolucizumab (0.05 ml solution) is to be administered every 4 weeks (monthly) for the first 3 doses. Thereafter, the Investigator may individualize treatment intervals based on the disease activity in the study eye as assessed by visual acuity and/or anatomical parameters (BCVA and/or IRF,

SRF, sub-RPE fluid, hemorrhage, CRT and/or OCTA parameters and/or 3-field CFP). A first disease activity assessment is to be performed at Week 16, as recommended in Beovu® SmPC. In participants without disease activity, treatment every 12 weeks (q12w) should be considered. In patients with DA, treatment every 8 weeks (q8w) should be considered. Disease activity will be first assessed at Week 16 and then at each subsequent scheduled q12w/q8w treatment visit. In participants on q12w regimen with disease activity at any of these visits, a q8w treatment regimen should be considered. In participants on q8w regimen without disease activity for two consecutive treatment visits in the opinion of the Investigator, the re-allocation to a q12w regimen should be considered. Figure 2.3.1-1 provides a graphical summary of the study drug administration during the study.

Figure 2.3.1-1: Treatment regimen



Regardless of treatment administration, Baseline, Week 4, Week 8, Week 12, Week 16 and Week 48 visits are mandatory for all participants. The timepoints of the other treatment visits will depend on the treatment regimen of each participant (q12w/q8w).

For all participants, the last potential study treatment will be at the Week 44 visit or at the Week 48 visit, according to the different treatment regimen implemented.

3.3.2. Method of Assigning Patients to Treatment Groups

This is a single arm study all eligible participants are to be assigned to IVT brolucizumab 6 mg treatment at Baseline.

The Investigator will confirm that the participant has fulfilled all the inclusion/exclusion criteria in the source documents and the appropriate page on the eCRF. The Investigator will then assign the participant to treatment.

3.3.3. Prior and Concomitant Therapy

No control drug or other treatments beyond investigational drug are included in this trial.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate page in the electronic Case Report Form (eCRF).

During the study, standard of care or other treatments according to the Investigator's practice for wAMD and other diseases in the fellow eye are permitted at any time and must be recorded in the appropriate eCRF page. Treatment of the fellow eye must be scheduled in a way not to disturb the schedule for visits and treatments in the study eye. The fellow eye must be monitored according to routine practice and adverse events (AEs) captured in the eCRF.

Corticosteroids administered via intra-nasal, inhaled, intra-articular or non-extensive dermal route (< 20% total body surface area) are permitted during the study. For other routes of corticosteroid administration, refer to *Section 6.2.2 Prohibited medication* of the study protocol.

If cataract surgery is necessary, attempt to schedule cataract surgery ≥ 7 days after the most recent study treatment. Study treatment may be resumed ≥ 14 days after cataract surgery, assuming an absence of surgically related complications.

If yttrium aluminum garnet (YAG) laser is necessary, it should be performed ≥ 7 days prior to the scheduled study visit.

If vitrectomy is necessary in the study eye, it should be attempted to schedule the surgery ≥ 14 days after the most recent study treatment. Study treatment may be given during vitrectomy surgery if deemed necessary according to investigator's discretion.

If the subject is planning to receive a COVID-19 vaccine that is authorized by local regulation, it is recommended to receive the vaccine at least 7 days before or after the study treatment visit including Baseline (Day 1) visit.

A detailed list of prohibited medications in study eye, in fellow eye and systemic treatments is provided in *Table 6-2 Prohibited medication and procedures* of the study protocol.

No rescue medication for wAMD in the study eye is foreseen. In case of lack of efficacy with investigational drug for wAMD and if the Investigator deems it is in the best interest of the patient to receive prohibited treatment in the study eye, the Investigator should follow the instructions for study treatment discontinuation or study discontinuation.

3.4. Schedule of Time and Events

The flowchart of the assessments schedule is reported in Figure 2.4-1 below.

Figure 2.4-1: Assessment schedule

Period	Screening	Treatment						End of Study
Visit Name	Screening*	Baseline Day 1	W4	W8	W12	W16	Treatment visits	W48*
Visit number	1	2	3	4	5	6	7-13	14
Weeks	Up to 2 weeks	1	4	8	12	16	20 to 44[1]	48
Obtain informed consent	X							
Demography	X							
Inclusion/ exclusion criteria	X	X						
Relevant medical history/current medical history	X							
Vital Signs[2, 3]	X	X	X	X	X	X	X	X
Prior/ Concomitant systemic medications	X	X	X	X	X	X	X	X
Prior/ Concomitant ocular medications	X	X	X	X	X	X	X	X
Serum β-hCG Pregnancy Test[4]	X							
Urine Pregnancy Test[4]		X	X	X	X	X	X	X
BCVA score (ETDRS)	X	X	X	X	X	X	X	X
IOP measurement[5]	X	X	X	X	X	X	X	X
Complete ophthalmic examination[2, 6]	X	X	X	X	X	X	X	X
SD-OCT[9]	X	X	X	X	X	X	X	X
OCTA	X	X	X	X	X	X	X	X

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Period	Screening	Treatment						End of Study
Visit Name	Screening*	Baseline Day 1	W4	W8	W12	W16	Treatment visits	W48*
Visit number	1	2	3	4	5	6	7-13	14
Weeks	Up to 2 weeks	1	4	8	12	16	20 to 44[1]	48
FA[9]	X							X
ICGA	X							X
Color Fundus Photography (CFP)[redacted]	X	X	X	X	X	X	X	X
EQ-5D-5L		X						X
HADS		X						X
Disease Activity Assessment[7]						X	X	X
Study drug administration		X	X	X		X[8]	X[8]	X[8]
Adverse Events	X	X	X	X	X	X	X	X

X = assessment to be recorded in the clinical database or received electronically from a vendor

* At Screening and Week 48 the fellow eye will be assessed for BCVA, ophthalmic examination, IOP, SD-OCT, OCTA, CFP, FA and ICGA. For the other visits it will be assessed according to clinical practice

[1] Treatment visits will take place every 8 or 12 weeks starting from Visit 4 (Week 8), according to Investigator's decision at each assessment visit

[2] Vital signs collection and/or complete ophthalmic examination are to be performed at each visit. The Investigator have to exclude the presence of any active intraocular inflammation in the study eye.

[3] Vital signs include sitting blood pressure and pulse rate.

[4] Women of childbearing potential only. A positive urine test should be confirmed by a Serum β-hCG Pregnancy test.

[5] IOP measurement is to be performed prior and 30-60 minutes after each treatment IVT injection

[6] Complete ophthalmic examination include slit lamp exam, IOP measurement and fundus exam, for safety assessment before and after IVT. Pupil dilation optional according to local practice.

[7] Disease activity assessment to be performed by the Investigator based on BCVA and/or one or more anatomical parameters detected by SD-OCT among IRF, SRF, sub-RPE fluid, hemorrhage and CRT, and/or OCTA parameters and/or 3-field CFP, as per clinical practice. Of note, only which of these functional and/or anatomical parameters the Investigator considered to assess disease activity will be recorded in the eCRF.

[8] Treatment according to Investigator's decision on treatment regimen (q12w or q8w) based on disease activity assessment.

[redacted]

The planned study visit schedule will be established at Baseline/Day 1 (first day of treatment) for all participants. All subsequent scheduled visits will be calculated based on the Day 1 visit date. The mandatory post-Baseline visits of the study are Week 4, Week 8, Week 12 (no injection visit), Week 16 and Week 48. After Week 16, the treatment visit intervals will be determined by the Investigator, based on the patient's disease activity.

A ± 7-day visit window is allowed, except for Baseline/Day 1. For a given protocol visit (except for Baseline), assessments can be performed on two consecutive days, provided both days are within the ± 7-day visit window.

Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the study visit at which the per-protocol assessments have taken place (except Baseline, in which case study treatment administration should occur within the next 24 hours). Two consecutive study treatments should be at least 21 days apart. For all visits, efficacy assessments and safety assessments should be performed prior to any administration of study treatment.

Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

If the COVID-19 pandemic limits or prevents on-site study visits, study treatment could not be administered, and other study assessments may not be performed. Alternative methods of safety monitoring may be implemented. Depending on local regulations, site capabilities and patient's visit status in the study, phone calls or virtual contacts (e.g., teleconsulting) can be performed for safety follow-up for the duration of the pandemic, until it is safe for the participant to visit the site again.

3.5. Sample Size and Power Estimation

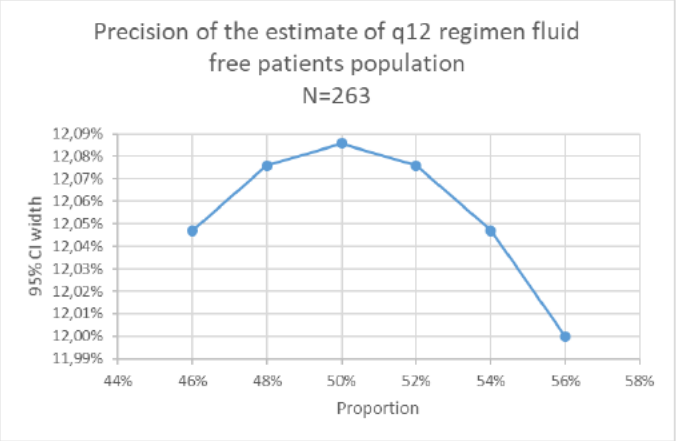
The sample size calculation is based on the assumption of an expected percentage of participants who have maintained the q12w regimen up to Week 48 equal to 56%, as derived from the HAWK study, and the hypothesis of a maximum percentage of not-fluid free participants out of these q12w-regimen participants at Week 48 equal to 18%. Therefore, the percentage of responders, defined as fluid-free participants who have maintained a q12w stable regimen up to Week 48, could range between 56% to 46%.

Considering a percentage of responders of 56% and a maximum width of the 95% confidence interval of 12%, 263 patients should be enrolled. Applying the rules of thumb, with 263 patients and a percentage of responders of 56%, a maximum number of 12 covariates can be included in the multivariate regression model (Harrell, 2015). As shown in Figure 2.5-1, the precision of the estimate remains stable around 12%, considering a percentage of responders ranging between 56% to 46%. Similar considerations can be made with a number of covariates that remains equal to 12.

Finally, to account for a screening failure rate of 12%, a total of approximately 300 participants should be screened in order to enroll 263 evaluable participants.

The sample size calculations were performed with nQuery 7.0.

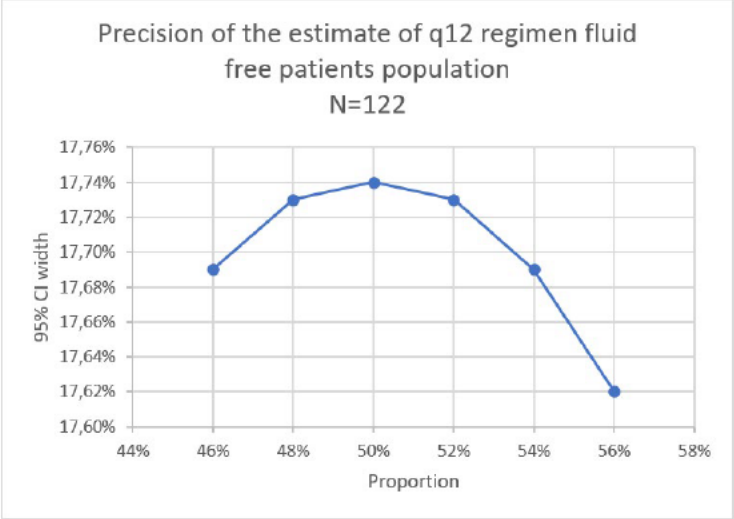
Figure 2.5-1: Precision of the estimate scenario



Since the enrolment was closed with less than 263 enrolled patients, the precision of the 95% CI will be re-computed based on the effective number of patients evaluable for the primary endpoint of the study.

Based on interim analysis, 122 enrolled patients will be available and consequently, the Figure above is recomputed according to the effective number of enrolled patients and provided below in Figure 2.5-2:

Figure 2.5-2: Precision of the estimate scenario re-computed



Based on different scenario of expected proportion between 46% to 56% and the effective number of 122 enrolled patients, the maximum width that can be observed will be of 17.74%.

4. DEFINITIONS AND GENERAL METHODOLOGY

4.1. General Methodology

Statistical tables, listings and analyses will be produced using SAS® release 9.4 (64 bit) or later (SAS Institute, Inc., Cary, NC, USA).

The data from all sites will be pooled and summarized.

Continuous data will be summarized with mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables. The percentage calculation will be based on total values (i.e., count will be shown also in the missing category, unless otherwise specified).

Unless stated otherwise, a two-sided alpha level 0.05 will be considered. No alpha level adjustment will be carried out for primary and secondary outcome variables, unless otherwise specified.

4.2. Definitions

Study Phases

The following phases are identifiable:

- Screening period: Day -14 to Day -1

Period of up to 2 weeks before baseline used to assess patient eligibility. The screening period starts with the signing of the informed consent.

One time re-screening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient.

Patients must have confirmed wAMD at Screening.

- Treatment: Day 1 to Week 48

At the Baseline visit (Day 1), after confirmation of eligibility, patients will be included and treated with intravitreal (IVT) brolucizumab at the dose of 6 mg. Only one eye could be treated in the study. Participants will receive three monthly loading doses of brolucizumab 6 mg at Baseline, Week 4 and Week 8, followed by a maintenance regimen every 12 weeks (q12w) or every 8 weeks (q8w) based on the absence/presence of disease activity (DA) in the study eye detected according to Investigator's decision based on the disease activity assessments (DAAs) of visual and/or anatomical outcomes performed by

the Investigator him/herself ("q12w/q8w regimen"). This period started with the first treatment administration (day 1) and ended at the last injection planned that could be at the Week 44 visit or at the Week 48 visit, according to the different treatment regimen implemented.

- End of Study

Week 48 visit, regardless the different treatment regimen implemented will constitute the end of study visit.

Management of Screening and Baseline visits on the same day

In case the protocol deviation "OTH027: Baseline - Day 1 (Week 1) visit performed on the same day of the Screening visit" will be detected, results reported at baseline visit will be considered also for screening visit. In fact, in this case data for assessments planned both at screening and at baseline visits will be recorded in the baseline one while assessments planned only at screening will be recorded in the screening visit.

Definition of Screening Failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, and Inclusion/Exclusion eCRF pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening phase.

Definition of Baseline

Baseline date (day 1) is defined as the date of the first treatment administration, i.e. the date of Visit 2.

First/Last Administration of Study Treatment

The date of first brolucizumab administration is the first date of injection reported in the BROLUCIZUMAB DOSAGE ADMINISTRATION RECORD eCRF page.

The date of last brolucizumab intake is the last treatment date reported in the TREATMENT DISPOSITION eCRF page.

Study day

Study day is defined as the number of days from the first treatment administration date (i.e., reference date) to the visit/event date. If the visit/event date is on the same day of after the reference date, it is calculated as:

Study day = Visit/event date - first brolucizumab administration date + 1 day.

If the visit/event date is before the first brolucizumab injection date, then the study day is calculated as follows:

Study day = Visit/event date - first brolucizumab administration date.

4.3. Coding of Therapies and Medical Terms

Medications reported in PRIOR AND CONCOMITANT MEDICATIONS eCRF pages will be coded using version B3_Q1_2022 of the World Health Organization (WHO) dictionary. Medical terms reported in the medical history/current medical conditions, surgical and medical procedures or adverse event are coded using version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

Versions of the dictionaries can be upgraded during the study according to Sponsor's request.

4.4. Handling of Drop-Outs or Missing Data

4.4.1. Missing or Partial Dates

All events with a start date on or before the data cut-off date and with an end date after the cut-off date will be reported as "continuing at the interim analysis". This rule also applies to events starting on or before the cut-off date but not having a documented end date. This approach is applicable to adverse events, concomitant medications, current medical conditions, current surgical and medical procedures and brolucizumab administration reports.

For incomplete dates, the imputation will be performed according to the following rule:

- If the date is completely missing, no imputation will be performed;
- In case of day missing, the day will be replaced with 15;
- In case of day and month missing, the day will be replaced with 1, the month with July.

These rules will be applied for wAMD diagnosis in right/left eye and for start/end date for prior/concomitant medications. Imputed dates must be checked for being in

acceptable logical sequence with other dates. If these rules lead to negative time from wAMD diagnosis to informed consent signature, the informed consent signature date was considered as date of wAMD diagnosis.

4.4.2. Handling of Missing Data/Imputation/Censoring Rules

For the primary endpoint, patients who prematurely discontinued the study should be considered as not being q12w fluid-free at Week 48.

The following missing Imputation Rules should be considered for the secondary endpoints:

- The last observation carry-forward (LOCF) method will be used to handle Missing data.
- As observed approach will be also considered.

Censoring rules will be applied for the time to sustained dryness and described in the section 6.3.2.4 of the present document.

4.4.3. Handling of Drop-Out Patients

Drop-out patients will be included in the analysis based on available assessments.

4.5. Multiple Comparison/Multiplicity

Not applicable.

4.6. Multicentre Studies/Center Pooling

The study will be conducted at about 30 Italian centers. The data from all centers will be pooled and summarized.

5. ANALYSIS POPULATIONS

The following analysis populations will be defined for statistical analysis:

- **Screened Set**: all participants who signed the informed consent.
- **Enrolled Set**: all screened patients who completed the screening defined as eligible patients both at Screening and at Baseline.
- **Full Analysis Set (FAS)**: all enrolled participants who completed the Baseline visit.
- **Safety Set**: all FAS participants who received at least one dose of the study drug.

6. STATISTICAL METHODOLOGY

6.1. Study Patients

An illustration of screening disposition will be provided on screened patients, providing the number of screened (i.e., patients who signed informed consent) and re-screened patients, the number of patients who completed the screening defined as eligible patients both at screening and baseline (i.e., patients for whom the question "Will the subject continue into the study?" = YES in the INCLUSION/EXCLUSION CRITERIA eCRF page and the question "Is the subject eligible for study based on the re-check of inclusion and exclusion criteria requirements?" = YES in the INCLUSION / EXCLUSION CRITERIA RE-CHECK eCRF page) and the number who discontinued the screening (i.e., patients not completed) together with the reason for screening discontinuation as reported in the STUDY DISPOSITION eCRF page. In addition, the reason for screen failure will be also tabulated according to the inclusion/exclusion criteria violated and the specific reported by Investigator in the STUDY DISPOSITION eCRF page. Of note, in case of presence of re-screened patients, they will be described according to their last evaluation.

A description of patient disposition will be provided on the enrolled patients providing both treatment and study patient status. Treatment status will be described based on TREATMENT DISPOSITION eCRF page specifying the number of patients who completed the treatment, the number of patients who are still on treatment and the number of patients who discontinued the study treatment will be summarized together with reason for treatment discontinuation. Similarly, study disposition will be described based on STUDY DISPOSITION eCRF page specifying the number of patients who completed the study, the number of patients who are still ongoing and the number of patients who discontinued with the reason for discontinuation. In addition, the number of enrolled patients entered at each visit will be provided.

The numerousness of the analysis populations will also be described and the reasons for excluding a patient from an analysis population will be provided on enrolled patients.

Protocol deviations will be summarized for the enrolled patients. Only Confirmed Clinical Study Report (CSR)-reportable protocol deviations will be included in the analysis. Non-protocol deviations (i.e., criteria leading to the exclusion from an analysis population, even if they do not themselves constitute a deviation from the study protocol) will be also summarized on enrolled patients. The Non-protocol deviation considered for this study is listed in Table 5.1-1.

Table 5.1-1: List of non-protocol deviations

Deviation code	Description	Exclusion from analysis population
NOPD01	Patient who did not receive any dose of study drug	SAF

NOPD=Non-protocol deviation; SAF=Safety Set.

All protocol and non-protocol deviations observed will be also listed.

6.2. Background and Demographic Characteristics

Demographic and other baseline data including disease characteristics evaluated at Screening/Baseline will be summarized for Safety set. In particular:

- **Demography data** will include age (years), sex, ethnicity and race.

- **History of primary diagnosis of wet Age-related Macular Degeneration (wAMD)** will provided, the time from wAMD diagnosis in study eye to informed consent signature date computed in months as (informed consent date – wAMD diagnosis date +1)/30.4375. In addition, the proportion of patients with bilateral disease (i.e., presence of wAMD also in fellow eye) will be provided together with time from wAMD diagnosis in fellow eye to informed consent for patients with wAMD also in the fellow eye.

- **Type of CNV lesion** at baseline will be described considering both possible combination of type of macular neovascularization (MNV) and the predominant type of MNV that could be Type I, Type II, Type III, PCV, UNG/P or UNG/Q.

- **Ocular medical and surgical history** will be summarized, by System Organ Class and Preferred Term according to the MedDRA dictionary, presenting the number and percentage of patients with at least one ocular medical and surgical history finding (i.e., reported in the ocular medical history category of MEDICAL HISTORY/CURRENT MEDICAL CONDITIONS eCRF page) considering separately relevant medical/surgical history, i.e. conditions reported as 'Not ongoing', and current medical/ surgical condition, i.e. conditions reported as 'Ongoing'. The ocular condition will be summarized overall and according to the study and fellow eye. Of note, the same condition could be reported for both eye and consequently will be count once for study eye, once for fellow eye and only once in the total column. In case of condition for which the eye is 'Unknown', it will be summarized in the overall column and in an addition unknown column.

- **Non-ocular medical and surgical history** will be summarized by System Organ Class and Preferred Term according to the MedDRA dictionary, presenting the number and percentage of patients with at least one non-ocular medical and surgical history finding (i.e., reported in the non-ocular medical history category of MEDICAL HISTORY/CURRENT MEDICAL CONDITIONS eCRF page) considering separately relevant medical/surgical history, i.e. conditions reported as 'Not ongoing', and current medical/ surgical condition, i.e. conditions reported as 'Ongoing'.

- **Fluorescein Angiography (FA) at screening** will be described considering the following parameters assessed in the study eye:
  - Total lesion size: the lesion associated with CNV will be described reporting the proportion of patients for whom the area is 'Evaluable' (i.e., the numeric measure should be present), 'Cannot grade (unreadable)', 'Not available (missing FA)' or 'Not applicable (=absent/no CNV)'. For patients with evaluable measurement, the area of lesion associated with CNV (mm^2) will be summarized with descriptive statistics for continuous data.
  - Total CNV size: the CNV within a lesion will be described reporting the proportion of patients for whom the area is 'Evaluable' (i.e., the numeric measure should be present), 'Cannot grade (unreadable)', 'Not available (missing FA)' or 'Not applicable (=absent/no CNV)'. For patients with evaluable measurement, the area of CNV within a lesion (mm^2) will be summarized with descriptive statistics for continuous data.

  The proportion of patients who performed the FA imaging also in the fellow eye will be provided even if these parameters will not grade.

  A description for the FA imagines' quality will be also provided reporting the proportion of images with quality concerns present and a description of the issue detected that could be one or more of the following:

  - NOT PER PROTOCOL
  - POOR FOCUS
  - POOR CONTRAST
  - UNDEREXPOSED
  - OVEREXPOSED
  - POOR FIELD PLACEMENT
  - NO TIMER INFORMATION
  - OTHER/ADDITIONAL DETAILS

  Similarly, the proportion of imagines with quality concerns that prevent any grading is provided together with the issue(s) detected (one or more than one among the list previously described).

- **Color Fundus Photography (CFP) at screening** will be described considering the following qualitative parameters assessed in the study eye:
  - Intra-Retinal hemorrhage-inner subfield
  - Intra-Retinal hemorrhage-central subfield
  - Sub-Retinal hemorrhage-inner subfield
  - Sub-Retinal hemorrhage-central subfield
  - Fibrosis-inner subfield
  - Fibrosis-central subfield
  - Drusen

  The presence/absence of these parameters will be described considering the values 'No', 'Yes', 'UNG/P', 'UNG/Q'. The proportion of patients who performed the CFP imaging also in the fellow eye will be provided even if these parameters will not grade.

  A description for the CFP imagines' quality will be also provided reporting the proportion of images with quality concerns present and a description of the issue detected that could be one or more of the following:

  - POOR FOCUS
  - POOR FIELD PLACEMENT
  - NOT PER PROTOCOL
  - POOR COLOR BALANCE
  - OVEREXPOSED
  - UNDEREXPOSED
  - UNDERSATURATED
  - OVERSATURATED
  - OTHER/ADDITIONAL DETAILS

  Similarly, the proportion of imagines with quality concerns that prevent any grading is provided together with the issue(s) detected (one or more than one among the list previously described).

- **Prior medications** are defined as therapies starting prior to the study and ending prior to the first brolucizumab administration. Non-ocular prior medications will be described by ATC code (2nd level class) and Preferred Term, presenting the number and percentage of patients taking at least one non-ocular prior medication. In addition, a focus on ocular prior medications (i.e., condition reported in the ocular category of PRIOR AND CONCOMITANT MEDICATIONS eCRF page) will be also provided overall and according to the study and fellow eye. Of note, the same medication could be reported for both eye and consequently will be count once for study eye, once for fellow eye and only once in the total column. In case of condition

for which the eye is 'Unknown', it will be summarized in the overall column and in an addition unknown column.

6.3. Efficacy Evaluation

6.3.1. Primary efficacy analysis

Definition of primary endpoint

The primary aim of the study is to assess which early anatomical parameters measured by multimodal imaging at each visit from Baseline to Week 16, predict in brolucizumab-treated participants with wAMD the q12w fluid-free response at Week 48.

The primary estimand of the study is to identify the q12w fluid-free predictive factors.

Patient will be classified as follows for the outcome of interest:

- **q12w fluid-free:** patients completing the treatment and the study maintaining a stable q12w regimen assigned at Week 16 up to Week 48 and without the presence of IRF and SRF at Week 48 according to SD-OCT grading.
- **not q12w fluid-free:**
  - patient who completes the treatment and the study with the presence of IRF or the presence of SRF at Week 48 according to SD-OCT grading;
  - patient who followed the q8w regimen of treatment at any time during the study (considering also who started with q12w regimen but then due to disease activity shifted to q8w regimen);
  - patient who discontinued treatment at any time after baseline since also the discontinuation from the treatment can be considered as intercurrent event and according to data handling rules should be considered as 'failure'.
  - patient who dropped out at any time after baseline since the discontinuation from the study is considered as intercurrent event and according to data handling rules should be considered as 'failure'.

The following qualitative and quantitative anatomical parameters measured by FA, ICGA, CFP and SD-OCT will be considered as potential predictive factors in the statistical model and, when measured at more than one timepoint, categories variables based on their changes between baseline and Week 16 will be created as described below:

Variable	Timing of data collection	Source	Categories used in the model	Reference value for the model
Type of predominant CNV lesion	Screening	CRC grading based on SD-OCT, FA, ICGA and CFP at Screening	Type I, Type II, Type III, PCV, UNG/P or UNG/Q. Of note, Type I and PCV will be considered as unique category while UNG/P and UNG/Q will be considered as missing data.	Type I + PCV
subRPE fluid	Baseline, Week 4, Week 8, Week 12 and Week 16	SD-OCT grading	Stable absent (i.e., all measurement 'No), Stable present (i.e., all measurement 'Yes'), Improved (i.e., last measurement collected as 'No' and baseline 'Yes'), Worsened (i.e., last measurement collected 'Yes' and baseline 'No').	Stable absent
SHRM	Baseline, Week 4, Week 8, Week 12 and Week 16	SD-OCT grading	Stable absent (i.e., all measurement 'No), Stable present (i.e., all measurement 'Yes'), Improved (i.e., last measurement collected as 'No' and baseline 'Yes'), Worsened (i.e., last measurement collected 'Yes' and baseline 'No').	Stable absent
ORT	Baseline, Week 4, Week 8, Week 12 and Week 16	SD-OCT grading	Stable absent (i.e., all measurement 'No), Stable present (i.e., all measurement 'Yes'), Improved (i.e., last measurement collected as 'No' and baseline 'Yes'), Worsened (i.e., last measurement collected 'Yes' and baseline 'No').	Stable absent
ELM integrity loss in center 1mm	Baseline, Week 4, Week 8,	SD-OCT grading	Stable absent (i.e., all measurement 'No), Stable present (i.e., all measurement	Stable absent

	Week 12 and Week 16		'Yes'), Improved (i.e., last measurement collected as 'No' and baseline 'Yes'), Worsened (i.e., last measurement collected 'Yes' and baseline 'No').	
Type of PED	Baseline, Week 4, Week 8, Week 12 and Week 16	SD-OCT grading	Stable Fibrovascular only (i.e. all measurement 'Fibrovascular only'), Stable not only fibrovascular (i.e. all measurement 'Predominantly fibrovascular' or 'Predominantly serous' or 'Drusenoid PED'), 'From Fibrovascular only to not only fibrovascular' (i.e., last measurement collected 'Predominantly fibrovascular' or 'Predominantly serous' or 'Drusenoid PED' and baseline 'Fibrovascular only'),), 'From not only fibrovascular to Fibrovascular only' (i.e., last measurement collected 'Fibrovascular only' and baseline 'Predominantly fibrovascular' or 'Predominantly serous' or 'Drusenoid PED').	Stable Fibrovascular only
CST (µm)	Baseline, Week 4, Week 8, Week 12 and Week 16	SD-OCT grading	Percentage changes in CST vs baseline at the last measurement collected.	NA

NA=Not Applicable; CNV=Choroidal Neovascularization; UNG/P=Ungradable due to pathology; UNG/Q=Ungradable due to quality SHRM=Subretinal hyper reflective materia; ORT=Outer retinal tubulation; ELM=External Limiting Membrane; CST=Center Subfield Thickness; PED=Pigment Epithelial Detachment.

Of note, for each variable 'Missing' values can be present in case that images are collected but not graded by Central Reading Center (CRC) since they are collected by means of a not certificated instrument.

Analysis methodology

Firstly, the proportion of patients with and without q12w fluid-free will be provided and then a descriptive summary table by q12w fluid-free and not q12w fluid-free will be provided for each variables described in table above.

A logistic models will be performed for each one of the variables listed above considering as outcome the patients' classification in q12w fluid-free and not q12w fluid-free.

Multivariable logistic model will be performed considering as outcome the patients' classification in q12w fluid-free and not q12w fluid-free and as covariates all the variables with $p<0.10$ in the previous analysis. Results of logistic models will be presented in terms of beta coefficient and standard error, Odds Ratio and relative 95% Confidence interval and p-value.

All these analyses will be performed on Safety population.

Data handling rules

In case of patients who dropped out at any time after baseline, the primary outcome cannot be evaluated since the patient status related to treatment regimen and presence of IRF o SRF at Week 48 are not observed. The dropped-out patients constitute intercurrent event and they will be considered a not q12w fluid-free at Week 48. Similarly, in case of patients who discontinued the treatment at any time after baseline, the primary outcome cannot be totally evaluated since the patient treatment regimen at q12w cannot be observed until Week 48. The patients who discontinued treatment constitute intercurrent event and they will be considered a not q12w fluid-free at Week 48.

Sensitivity of primary analysis

1) To investigate the robustness of the primary analysis with respect to a potential selection bias due to dropouts, a weighted multivariable logistic model will be applied to provide a robust inferential procedure for the analysis of predictors of patients' responses in presence of missingness. Since excluding participants because of missing values could introduce a selection bias, in order to restore the complete-case analysis to its original sample representation, each complete participant will be weighted for the inverse of his/her missingness probability. Firstly, the missingness probability will be estimated by means of a multivariable logistic model in which the outcome variable will be the drop-out status (i.e., 1=patient drop-out; 0=patient who complete the study) and the covariates included will be the following baseline variables: age, sex, time from wAMD diagnosis in study eye to Informed consent (months), type of predominant CNV lesion, CST, BCVA EDTRS score. Secondly, the weighted multivariable logistic regression with the same covariate selected for the multivariable model

previously described will be performed using the inverse missingness probability as weight. Of note, only patients with no missing data for each covariate included in the model can be considered in this analysis.

6.3.2. Secondary efficacy analysis

All secondary efficacy analyses will be based on the Safety Set. The analyses performed at eye level will focus on the study eye only.

6.3.2.1. Optical coherence tomography angiography (OCTA) parameters

Definition

Optical Coherence Tomography Angiography (OCTA) is a non-invasive imaging modality that provides cross-sectional, three-dimensional and high-resolution imaging of the retinal and choroidal vasculature with micrometer-scale depth resolution. It does not require any dye injection and allows the retinal and choroid vessels to be viewed dynamically.

Optical Coherence Tomography Angiography (OCTA) images will be obtained and assessed in the study eye at every study visit and in the fellow eye at Screening and Week 48. The OCTA images will be evaluated by the CRC considering only images on study eye during the study (except screening visit). The OCTA images on fellow eye and on study eye at screening will be only stored but not grading.

On OCTA images grading by CRC, the following qualitive parameter will be measured:

- Branching vessels: evaluate the width of vessel respect to previous read. The presence of tiny vessels branching from bigger vessels is indicative an active CNV lesion. The possible values will be 'increased from prior' (i.e., possible active CNV lesion), 'decreased from prior', 'stable', 'N/A (baseline)' (of note, this will be expected for baseline since there is not a previous image to be compare), 'UNG/P', 'UNG/Q'.
- Peripheral Anastomotic Arcades: possible values will be 'No', 'Yes', 'UNG/P', 'UNG/Q' and in case of presence (i.e., 'Yes') of peripheral anastomotic arcades at the vessel termini is indicative of an active CNV lesion.
- Vascular Loops: possible values will be 'No', 'Yes', 'UNG/P', 'UNG/Q'. The presence of vascular loop (i.e., anatomical anomalies) is indicative of an active CNV lesion.
- Dark Halo: possible values will be 'No', 'Yes', 'UNG/P', 'UNG/Q'. The presence of dark halo that are hypointense area considered as a region of choriocapillaris alteration, corresponding to local flow impairment and is indicative of an active CNV lesion.

In addition, the presence of CNV lesion is evaluated and described according to the following possible values: 'No', 'Yes', 'UNG/P', 'UNG/Q'. If CNV lesion is present, a description of its involvement of the foveal center will be provided always based on the values 'No', 'Yes', 'UNG/P', 'UNG/Q' together with details about the following quantitative parameters:

- CNV flow size: visualized by calculating the decorrelation of signal amplitude from consecutive B-scans, thus creating a contrast between static and non-static tissue, through an appropriate algorithm. To quantify the blood flow within the CNV, the CNV area and flow index were calculated from the 2D maximum projection outer retina CNV angiogram. The parameters related to CNV flow size are Total CNV lesion area (mm^2) and Greatest linear diameter of lesion (mm).
- Vessel density of the lesion: calculated as a ratio of the area occupied by vessels to the total area of the lesion that is reported as CNV vascular density (%).

Analysis methodology

Firstly, a description for the OCTA imagines' quality will be provided at each visit reporting the proportion of images with quality concerns present and a description of the issue detected that could be one or more of the following:

- NOT PER PROTOCOL/INCOMPLETE
- OFF-FOVEA
- MOTION ARTIFACT
- PROJECTION ARTIFACT
- SEGMENTATION ERROR
- DEGRADED IMAGE
- OTHER

Similarly, the proportion of imagines with quality concerns that prevent any grading is provided together with the issue(s) detected (one or more than one among the list previously described).

All qualitative and quantitative parameters described above will be described overall at each visit in terms of absolute and relative frequencies or as continuous variable, respectively.

For quantitative variables (i.e., Total CNV lesion area (mm^2) and Greatest linear diameter of lesion (mm) and CNV vascular density (%)), absolute changes from baseline will be computed and summarized at each visit. A paired t-test or Wilcoxon

signed rank test, based on data distribution, will be used to test the difference at each time point vs Baseline.

For all qualitative variables except Branching vessels (excluded since this variable provided as result the comparison to the previous read and not a status at each visit), shift table of each post-baseline visit vs Baseline will be provided. A McNemar test Test will be used to test the difference at each post-baseline visit vs baseline. Of note, shift tables will be provided considered only patients for whom baseline and post-baseline value are both available (i.e., parameter considered equal to 'No' or 'Yes').

Data handling rules

An observed approach will be considered for all the analysis.

Sensitivity of secondary analysis

Not applicable.

6.3.2.2. Spectral Domain Optical Coherence Tomography (SD-OCT)

Definition

OCT is a noninvasive imaging technique able to visualize structural changes of the neurosensory retina and the RPE through high-resolution cross-sectional (tomographic) images (B-scans). OCT systems based on the spectral domain technology, i.e. spectral-domain OCT (SD-OCT), allow dense scanning of the macula with an improved axial resolution and it allows to define the morphological features of the CNV complex, such as retinal thickening, and to detect early signs of CNV activity, such as intraretinal (IRF), subretinal (SRF) and under RPE (sub-RPE) fluid, intraretinal cystoid spaces and PED, as well as edema.

Spectral Domain Optical Coherence Tomography (SD-OCT) images will be obtained and assessed in the study eye at every study visit and in the fellow eye at Screening and at Week 48. Only SD-OCT machines can be used (i.e., no time-domain nor swept-source OCT). The SD-OCT images will be evaluated by the CRC considering only images on study eye during the study (except screening visit). The SD-OCT images on fellow eye and on study eye at screening will be only stored but not grading.

On SD-OCT images grading by CRC, the following qualitive parameter will be measured:

- Intraretinal fluid (IRF) that is the fluid that accumulates within the neurosensory retina due to the disruption of the external limiting membrane (ELM)-photoreceptor complex in the outer retina by the active CNV membrane. If IRF fluid was not absent (i.e., present or UNG/P or UNG/Q), also

the following subcategories will be graded: (1) IRF in center 1 mm (i.e., fluid in the central 1 x 1-mm subfield) and (2) IRF at foveal center. Of note, the second one will be evaluated only in case IRF in 1 mm was not absent (i.e., present or UNG/P or UNG/Q). The possible values of these parameters will be 'No', 'Yes', 'UNG/P', 'UNG/Q'.

- Subretinal fluid (SRF) that is the fluid that commonly accumulates between the neurosensory retina and the RPE due to the profuse leakage from blood vessels of the CNV complex. If SRF fluid was not absent (i.e., present or UNG/P or UNG/Q), also the following subcategories will be graded: (1) SRF in center 1 mm (i.e., fluid in the central 1 x 1-mm subfield) and (2) SRF at foveal center. Of note, the second one will be evaluated only in case SRF in 1 mm was not absent (i.e., present or UNG/P or UNG/Q). The possible values of these parameters will be 'No', 'Yes', 'UNG/P', 'UNG/Q'.
- Sub-retinal pigment epithelium (sub-RPE) fluid that is the fluid that accumulates under the RPE, thus often leading to PEDs. If sub-RPE fluid was not absent (i.e., present or UNG/P or UNG/Q), also the subcategory sub-RPE in center 1 mm (i.e., considering the central 1 x 1-mm subfield) will be graded. The possible values of these parameters will be 'No', 'Yes', 'UNG/P', 'UNG/Q'.
- Subretinal Hyperreflective Material (SHRM) that is a poorly defined, medium-to-hyperreflective mass between the neurosensory layers and the RPE on SD-OCT, which is indicative of the neurovascular membrane, particularly in type II CNV lesions, and of disciform scar formation. If SHRM was not absent (i.e., present or UNG/P or UNG/Q), also the following subcategories will be graded: (1) SHRM in center 1 mm (i.e., considering the central 1 x 1-mm subfield) and (2) SHRM at foveal center. Of note, the second one will be evaluated only in case SHRM in 1 mm was not absent (i.e., present or UNG/P or UNG/Q). The possible values of these parameters will be 'No', 'Yes', 'UNG/P', 'UNG/Q'.
- Outer Retinal Tubulation (ORT) that are branching tubular structures located in the outer nuclear layer of the retina, which seems to be indicative of a rearrangement of degenerating photoreceptors in a variety of retinal diseases, including wAMD. If ORT was not absent (i.e., present or UNG/P or UNG/Q) also the subcategory ORT in center 1 mm (i.e., considering the central 1 x 1-mm subfield) will be graded. The possible values of these parameters will be 'No', 'Yes', 'UNG/P', 'UNG/Q'.
- Status of the ELM as an indicator of retinal integrity will be evaluated focusing on ELM integrity loss in center 1 mm (i.e., considering the central 1 x 1-mm subfield). The possible values will be 'No', 'Yes', 'UNG/P', 'UNG/Q'.
- In the study protocol, the Volume of Pigment-Epithelium Detachment (PEDs) defined as irregularly elevated lesions produced by the growth of the choroidal neovascular membrane and the accumulation of fluid or material in the sub-RPE space. On SD-OCT, PEDs appear as broad elevations of the RPE

band relative to Bruch's membrane. The volume of PEDs is considered as a quantitative parameter evaluated by SD-OCT. However, it was not possible to measure this volume according to the CRC evaluation. Consequently, the following qualitative parameters will be provided: the presence of PED will be summarized considering the possible values (i.e., 'No', 'Yes', 'UNG/P', 'UNG/Q') and in case of PED presence, a description of the type of PED will be provided considering the predominant feature as fibrovascular only, predominantly fibrovascular, purely serous, predominantly serous, drusenoid PED, UNG/P, UNG/Q.

In addition, the following quantitative parameter will be measured:

- Central Retinal Thickness (CRT) measurement, as main quantitative morphological parameter of wAMD. The CRT evaluated in this study represents the average retinal thickness of the circular area within 1 mm diameter around the foveal center and it will be called as Center Subfield Thickness (CST) also known as foveal thickness and it will be measured in µm.

Analysis methodology

Firstly, a description for the SD-OCT imagines' quality will be provided at each visit reporting the proportion of images with quality concerns present and a description of the issue detected that could be one or more of the following:

- HIGH SPEED NOT HIGH RESOLUTION
- VOLUME SCAN ABSENT
- VOLUME SCAN INCOMPLETE
- RASTER/LINE SCAN ABSENT
- RASTER/LINE SCAN INCOMPLETE
- OFF-FOVEA
- MOTION ARTIFACT
- SCAN CLIPPING
- DEGRADED IMAGE
- POOR CONTRAST
- OTHER/ADDITIONAL DETAILS

Similarly, the proportion of imagines with quality concerns that prevent any grading is provided together with the issue(s) detected (one or more than one among the list previously described).

All qualitative and quantitative parameters described above will be described overall at each visit in terms of absolute and relative frequencies or as continuous variable, respectively.

For quantitative variables (i.e., CST (µm)), absolute changes from baseline will be computed and summarized at each visit. A paired t-test or Wilcoxon signed rank test, based on data distribution, will be used to test the difference at each time point vs Baseline. A spaghetti plot of CST values at each timepoint will be provided by type of predominant CNV lesion (of note, 'UNG/Q' and 'UNG/P' evaluation of predominant CNV lesion will be considered in a unique category 'Ungradable').

CST will also be described considering only patients with BCVA ETDRS score lower than 69 letters at baseline in terms of descriptive statistics together with absolute changes from baseline and by means of spaghetti plot.

For the qualitative variables IRF, SRF, sub-RPE, SHRM, ORT and ELM integrity loss a shift table of each post-baseline visit vs Baseline will be provided. A McNemar test Test will be used to test the difference at each post-baseline visit vs baseline. Of note, shift tables will be provided considered only patients for whom baseline and post-baseline value are both available (i.e., parameter considered equal to 'No' or 'Yes') and moreover, the measurements of these qualitative parameters in center 1 mm and at foveal center will not be considering for shift tables.

Data handling rules

An observed approach will be considered for all the analysis.

Sensitivity of secondary analysis

Not applicable.

6.3.2.3. Best corrected visual acuity (BCVA)

Definition

The visual acuity is assessed by means of Best corrected visual acuity (BCVA). BCVA measurements will be taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) like visual acuity testing charts at an initial testing distance of 4 meters. The ETDRS chart has been established as the gold standard for objective VA measurement in clinical trials and consists of 14 rows of 5 letters each, for a total of 70 letters. A higher score represents better vision. BCVA will be assessed in the study eye at every study visit and in the fellow eye at Screening and Week 48. Only assessment on the study eye will be considered in the analysis.

Analysis methodology

BCVA ETDRS score in the study eye will be summarized at each visit by means of descriptive statistics for continuous variable together with absolute changes from baseline. A paired t-test or Wilcoxon signed rank test, based on data distribution, will

be used to test the BCVA ETDRS score difference at each time point vs Baseline. A spaghetti plot of BCVA ETDRS score at each timepoint will be provided by type of predominant CNV lesion (of note, 'UNG/Q' and 'UNG/P' evaluation of predominant CNV lesion will be considered in a unique category 'Ungradable').

In addition, considering each post-baseline visit, the proportion of patients with improvement of at least 5, 10 and 15 letters in BCVA ETDRS score (i.e., absolute change greater or equal to 5, 10 and 15, respectively) will be provided. Similarly, the proportion of patients with worsening of at least 5, 10 and 15 letters in BCVA ETDRS score (i.e., absolute change less or equal to -5, -10 and -15, respectively) will be summarized.

The same analyses will be also repeated focusing on patients with BCVA ETDRS score at baseline lower than 69 letters.

Data handling rules

Firstly, an observed approach will be considered for all the analysis and the LOCF approach will be also applied but focusing only until Week 16 since after this timepoint the scheduled of visits will be different for each patient according to treatment regimen assigned.

Sensitivity of secondary analysis

Not applicable.

6.3.2.4. Sustained dryness

Definition

Firstly, the proportion of patients with fluid present at baseline will be identified as patients with IRF or SRF equal to "Yes" at baseline and it will be presented together with the distribution of patients in the following categories: patients with only IRF present at baseline, patients with only SRF present at baseline and patients with both IRF and SRF at baseline.

Among patients with fluid present at baseline, patients with fluid resolution will be identified in case of absence of IRF and SRF and patients without fluid resolution will be also categorized in 'Only IRF present', 'Only SRF present', 'Both IRF and SRF present' at each post-baseline applicable timepoint from Week 8 to Week 48 considering patients who performed SD-OCT at the corresponding timepoint. Then patients who achieved the sustained dryness will be identified considering patients with fluid resolution for at least 2/3 consecutive visits.

For each possible timepoint from Week 8 to Week 48, the sustained dryness will be evaluated considered the SD-OCT assessment as follows:

- If patient perform the visit: the assessment done at the specific timepoint and the previous one performed.
- If patient does not perform the visit: the previous 2 assessments performed will be considered.

The time to achieved sustained dryness is defines as the time, in weeks, from the first injection (i.e., baseline visit) to the earliest post-baseline SD-OCT assessment date on which the first sustained dryness is reached. If a patient does not achieve sustained dryness, the time will be censored at the date of last SD-OCT assessment.

Time to sustained dryness is computed as:

(event/censoring date – first injection date +1)/7

where event date is SD-OCT date in which the first sustained dryness is reached while censor date is the last SD-OCT date.

Analysis methodology

Firstly, a description of the proportion of patients with IRF or SRF present at baseline will be provided. On these patients a description of the proportion of patients with fluid resolution, defined as absence of IRF and SRF fluid, will be provided at each timepoint considered the number of patients who perform each visit. A graphical representation (bar graph) will be also provided.

The cumulative incidence rate of patients with sustained dryness from Week 8 up to Week 48 will be summarized together with 95% confidence interval (CI) using the Clopper-Pearson method. A graphical representation (bar graph) will be also provided.

The median time to achieve sustained dryness and its corresponding two-sided 95% confidence interval (CI) will be estimated using the Kaplan-Meier product-limit method. Reverse Kaplan-Meier plot will be also presented.

Data handling rules

An observed approach will be considered.

Sensitivity of secondary analysis

Not applicable.

6.3.2.5. Reason underlying the Investigators' choice of brolucizumab treatment regimen at Week 16

Definition

As previously investigated during the interim analysis, the reasons underlying the Investigators' choice of brolucizumab treatment regimen at Week 16 will be analyzed.

According to SmPC of brolucizumab, after the loading phase of treatment (i.e., first 3 injection every month) at Week 16 the investigator should choice the treatment regimen for each patient between the q12w or the q8w regimen. This choice should be based on the presence/absence of disease activity evaluated according to different parameters.

Analysis methodology

Considering the safety set and the number of patients who performed Week 16 and were still on treatment, a description of the total number of parameters considered to assess the presence or absence of disease activity at Week 16 will be provided in terms of continuous variable and frequencies of each combination of parameters considered to assess disease activity will be also provided (e.g., BCVA+CSR, CST+IRF and so on). Considering the total number of patients who performed Week 16 and were still on treatment, the proportion of patients for whom their disease activity is evaluated by means of each one of the following parameters is summarized:

- BCVA
- Leakage at FA/ICGA
- Central Subfield Thickness (CST) at SD-OCT
- Intraretinal fluid (IRF) at SD-OCT
- Subretinal fluid (SRF) at SD-OCT
- Subretinal pigment epithelium (sub-RPE) fluid at SD-OCT
- Retina Pigment Epithelial Detachment volume at SD-OCT
- Central Retinal Thickness (CRT)
- Subretinal hyperreflective material (SHRM) at SDOCT
- CNV size at OCTA
- Vessel density at OCTA
- Vessel morphology at OCTA
- Hemorrhage at CFP
- Other

A graphical representation of the proportion of patients with disease activity evaluated by means of each parameter will be also provided by means of graph bar.

These results (i.e., both proportion and bar graph) will be provided overall and according to the final regimen choice reported by the Investigator (i.e., q12w or q8w).

The parameters used for the regimen choice will be also classified in the following categories:

- BCVA
- Leakage at FA/ICGA
- SD-OCT parameters (i.e., Central Subfield Thickness (CST), Intraretinal fluid (IRF), Subretinal fluid (SRF), Subretinal pigment epithelium (sub-RPE) fluid, Retina Pigment Epithelial Detachment volume, Subretinal hyperreflective material (SHRM), Central Retinal Thickness (CRT))
- OCTA parameters (i.e., CNV size, Vessel density, Vessel morphology)
- Hemorrhage at CFP
- Other

The proportion of patients evaluated by means of each category will be described and graphically represented.

In addition, multivariate logistic regression model will also be implemented to evaluate which of these factors are determinants for the selection of the dosing regimen at Week 16. The response variable will be the treatment regimen assigned to each patient (q12w or q8w), while the covariates included in the model will be the categories of parameters used to take the regimen choice according to the group presented above.

Considering the safety set and the number of patients who performed Week 16 and were still on treatment, descriptive statistics of SD-OCT parameters and predominant type CNV lesion at baseline will be provided considering:

- BCVA groups based on BCVA changes at Week 12: 'BCVA improvement' if change from baseline at Week 12 was greater or equal to 5 letters, 'BCVA stable' if change from baseline at Week 12 was between -5 and +5 letters and 'BCVA worsening' if change from baseline at Week 12 was lower or equal to -5 letters.
- CST groups based on CST changes at Week 12: '<0' and '>=0'.

<u>Data handling rules</u>

No missing imputation will be performed.

<u>Sensitivity of secondary analysis</u>

Not applicable.

6.3.2.6. HADS questionnaire

Definition

The Hospital Anxiety and Depression Scale (HADS) is a fourteen-item scale that generates ordinal data. HADS is composed by seven items relate to anxiety and seven relate to depression. This patient-reported outcome measure was specifically developed to avoid reliance on anxiety/depression aspects which are also common somatic symptoms of illness, such as fatigue and insomnia or hypersomnia.

The HADS consists of two sub-scores: the HAD-A for anxiety and HAD-D for depression. For each sub-score, each related item is rated on a 4-point scale (from 0 to 3 points) as reported below.

The HAD-A sub-score for anxiety will be computed considering the following 7 items:

1. Item *1-A. I feel tense or 'wound up'*: scored as 'Most of the time' = 3 to 'Not at all' = 0.
2. Item *3-A. I get a sort of frightened feeling as if something awful is about to happen*: scored as 'Very definitely and quite bad' = 3 to 'Not at all' = 0.
3. Item *5-A. Worrying thoughts go through my mind*: scored as 'A great deal of the time' = 3 to 'Very little' = 0.
4. Item *7-A. I can sit at ease and feel relaxed*: scored as 'Not at all' = 3 to 'Definitely' = 0.
5. Item *9-A. I get a sort of frightened feeling like 'butterflies' in the stomach*: scored as 'Very often' = 3 to 'Not at all' = 0.
6. Item *11-A. I feel restless as if I have to be on the move*: scored as 'Very much indeed' = 3 to 'Not at all' = 0.
7. Item *13-A. I get sudden feelings of panic*: scored as 'Very often indeed' = 3 to 'Not at all' = 0.

The HAD-D sub-score for depression will be computed considering the following 7 items:

1. Item *2-D. I still enjoy the things I used to enjoy*: scored as 'Hardly at all' = 3 to 'Definitely as much' = 0.
2. Item *4-D. I can laugh and see the funny side of things*: scored as 'Not at all'= 3 to 'As much as I always could' = 0.
3. Item 6-D. I feel cheerful: scored as 'Never' = 3 to 'Most of the time' = 0.
4. Item 8-D. I feel as if I am slowed down: scored as 'Nearly all the time' = 3 to 'Not at all' = 0.
5. Item 10-D. I have lost interest in my appearance: scored as 'Definitely' = 3 to 'I take just as much care as ever' = 0.

6. Item 12-D. I look forward with enjoyment to things: scored as 'Hardly at all' = 3 to 'As much as I ever did' = 0.
7. Item 14-D. I can enjoy a good book or radio or television programme: scored as 'Very seldom' = 3 to 'Often' = 0.

The sum of the rating of the seven anxiety items will provided the HAD-A sub-score while the sum of the rating of the seven depression items will provided the HAD-D sub-score.

Each sub-score ranges from 0 to 21 points: scores ≥11 indicate the presence of an anxious or depressive disorder, scores between 8-10 points are borderline abnormal, and scores ≤7 indicate that an anxious or depressive disorder is not present.

Analysis methodology

Each HADS item will be summarized at each visit (i.e., Baseline and Week 48) providing absolute and relative frequencies of each level answer.

HAD-A and HAD-D score will be summarized at each visit by means of descriptive statistics for continuous variable together with absolute changes from baseline. A paired t-test or Wilcoxon signed rank test, based on data distribution, will be used to test the HAD-A and HAD-D score difference at Week 48 vs Baseline.

In addition, HAD-A and HAD-D will be evaluated according to the following categories:

- **Normal:** Score ≤ 7 points that indicates disorder not present
- **Borderline abnormal:** Score between 8-10 points
- **Abnormal:** Score ≥ 11 points that indicate the presence of anxious or depressive disorders

A shift table based on this classification will be provided to compare HAD-A and HAD-D at Week 48 respect to Baseline considering patients who completed HAD questionnaire both at baseline and at Week 48.

Data handling rules

No missing imputation will be performed.

Sensitivity of secondary analysis

Not applicable.

6.3.2.7. EQ-5D-5L questionnaire

Definition

The EQ-5D-5L is a standardized widely used instrument for measuring generic health status. It comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the five dimensions comprising the EQ-5D descriptive system is divided into five levels of perceived problems:

- LEVEL 1: indicating no problem
- LEVEL 2: indicating slight problems
- LEVEL 3: indicating moderate problems
- LEVEL 4: indicating severe problems
- LEVEL 5: indicating unable to/extreme problems.

A unique health state is defined by combining one level from each of the five dimensions (example: health state 11111 indicates no problems on any of the five dimensions). A total of 3125 possible health states is defined in this way. EQ-5D-5L health states can be summarized using the 5-digit code or represented by a single summary number (*index value*), which reflects how good or bad a health state is according to the preferences of the general population of a country/region. The EQ-5D-5L index value will be computed considering the Italian Finch et al value set Version 1.1 (updated January 26, 2022) as provided in the online analysis tool of EQ-5D for Italy country (refers to https://euroqol.org/support/analysis-tools/index-value-set-calculators/). The EQ-5D-5L index value can be computed only for patients who answered to all 5 dimensions and is computed as follows:

1. A weight is associate based on each dimensions answer considering the weight reported in table below:

		Dimensions				
		Mobility	**Self-care**	**Usual activities**	**Pain/ discomfort**	**Anxiety/ depression**
Answer	1: no problem	0	0	0	0	0
	2: slight problem	0.051	0.046	0.050	0.047	0.044
	3: moderate problem	0.064	0.056	0.064	0.088	0.109
	4: severe problem	0.244	0.216	0.225	0.353	0.318
	5: unable to/extreme problems	0.329	0.257	0.255	0.408	0.322

2. The utility score is computing summing each assigned weight across 5 domains
3. EQ-5D-5L index value is derived as 1 – utility score

For ease, considering a patient with heath state 12345 (i.e., patient who reported no problem for mobility, slight problem for self-care, moderate problem for usual activities, severe problem for pain/discomfort and extreme problems for anxiety depression) the utility index is the computed as 0 + 0.046 + 0.064 + 0.353 + 0.322 = 0.785 and consequently the EQ-5D-5L index value is equal to 1 – 0.785 = 0.215. Of note, the EQ-5D-5L index value can also be negative for some health state (i.e., 55555).

The EQ-5D-5L total score is determined through a Visual Analogue Scale (VAS) and ranges from 0 to 100 with higher scores indicative of a better health status.

Analysis methodology

Each EQ-5D-5L dimension will be summarized at each visit (i.e., Baseline and Week 48) providing absolute and relative frequencies of each level answer.

A graphical representation of each of the 5 dimensions will also be provided to show the frequencies of each level answer at baseline and at Week 48.

EQ-5D-5L index values and EQ VAS values will be summarized at each visit by means of descriptive statistics for continuous variable together with absolute changes from baseline. A paired t-test or Wilcoxon signed rank test, based on data distribution, will be used to test EQ-5D-5L index values and EQ VAS values difference at Week 48 vs Baseline.

Data handling rules

No missing imputation will be performed.

Sensitivity of secondary analysis

Not applicable.

[redacted]

6.3.4. Measurement of Treatment Compliance

As stated in section 6.6.1 "Treatment compliance" of study protocol, the evaluation of the exposure to the study treatment will be performed and it is described in section 6.4.1 of the present document. The compliance with the study treatment will be assessed by the Investigator at each visit. No formal computation of compliance will be applied since the route of administration necessarily requires the patient's presence on site and Investigator has to administer the drug to patient. All data collected related to injection will be listed.

6.4. Safety Evaluation

Safety assessments will include complete ophthalmic examination, including IOP measurement prior and after each IVT injection, and vital signs, as well as monitoring and recording type, frequency, and severity for all AEs.

The safety analysis will be performed on the Safety population.

6.4.1. Extent of Exposure

Exposure to the study treatment will be based on the number of IVT injections administered.

The exposure will be summarized as a continuous variable counted the total number of IVT injection taken by each patient. The exposure will be also described as categorical variable considering each injection category (e.g., 1 injection, 2 injection, etc.).

A status of treatment regimen assigned to patient will be described. Considering the number of patients who reached Week 16 visit, patients will be described according to the first regimen choice (i.e., q12w or q8w) and the evaluation of disease activity will be also provided within each group.

6.4.2. Concomitant medications

Concomitant medications are defined as therapies ending or ongoing after the first brolucizumab administration. Concomitant medications/ surgical and medical procedures will be described by ATC code (2nd level class) and Preferred Term, presenting the number and percentage of patients taking at least one concomitant medication/procedures. In addition, a focus on ocular concomitant medications (i.e., condition reported in the ocular category of PRIOR AND CONCOMITANT MEDICATIONS eCRF page) will be also provided overall and according to the study and fellow eye. Of note, the same medication could be reported for both eye and consequently will be count once for study eye, once for fellow eye and only once in the total column.

A medication with a missing start date will be assumed to be a concomitant medication, unless the stop date is before the first brolucizumab administration date, in which case the medication will be summarized as a prior medication. Medications with start dates before the first brolucizumab administration date and missing end dates or end dates after the first dosing date will be summarized as concomitant medications.

Moreover, surgical and medical procedures administrated to each patient will be described will be described by System Organ Class and Preferred Term, presenting the number and percentage of patients taking at least one surgical or medical procedure. In addition, a focus on ocular surgical and medical procedures (i.e., condition reported in the ocular category of SURGICAL AND MEDICAL PROCEDURES eCRF page) will be also provided overall and according to the study and fellow eye. Of note, the same medication could be reported for both eye and consequently will be count once for study eye, once for fellow eye and only once in the total column.

6.4.3. Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as Adverse Events (AEs) that occurs on-treatment period, i.e., with a start date after or on the same date of first administration of study treatment.

General rules for AE Reporting

TEAEs will be descriptively summarized, whether non-TEAEs will only be listed.

TEAE summaries will be presented by primary SOC and PT sorted in alphabetical order within each SOC using the MedDRA dictionary.

If a patient report more than one TEAE coded to the same PT, in the analysis the patient will be counted only once in the incidence calculation for that PT. Similarly, if a patient has more than one TEAE in the same SOC, the patient will be counted only once in the total number of patients with an TEAE for that SOC.

The following TEAE summaries will be produced:

- General summary of TEAEs including the total number of events and absolute and relative frequency of patients with respectively at least one event of the following categories: TEAEs, treatment-emergent serious adverse events (TESAEs), ocular TEAEs, non-ocular TEAEs, suspected drug-related TEAEs, TEAEs with relationship to ocular injection procedure, TEAEs leading to interruption of treatment (defined as events with Action taken with drug of interest equal to "Drug interrupted"), TEAEs leading to withdrawn of treatment (defined as events with Action taken with drug of interest equal to "Drug withdrawn"), TEAEs leading to study discontinuation, fatal TESAEs.
- Summary of all TEAEs by SOC and PT;
- Summary of all TEAES by SOC, PT and maximum severity.

- Summary of all suspected drug-related TEAEs by SOC and PT;
- Summary of all suspected drug-related TEAEs by SOC, PT and maximum severity.
- Summary of all TEAEs with relationship to ocular injection procedure by SOC and PT;
- Summary of all TEAEs leading to interruption of treatment by SOC and PT;
- Summary of all TEAEs leading to withdrawn of treatment by SOC and PT;
- Summary of all TEAEs leading to study discontinuation by SOC and PT;
- Summary of all fatal TEAEs by SOC and PT;
- Summary of all TESAEs by SOC and PT;
- Summary of all TESAES by SOC, PT and maximum severity.

In addition, focusing on ocular TEAEs, a general summary of these events and their description by SOC and PT will be also provided overall and according to the study eye and fellow eye. Of note, the same medication could be reported for both eye and consequently will be count once for study eye, once for fellow eye and only once in the total column.

Listings of deaths, fatal TEAEs, non-fatal TESAEs, suspected drug-related TEAEs, TEAEs with relationship to ocular injection procedure, TEAEs leading to interruption of treatment, TEAEs leading to withdrawn of treatment, TEAEs leading to study discontinuation will be provided. A listing of all non-treatment emergent adverse event will be also described.

6.4.4. Laboratory parameters

Not applicable.

6.4.5. Vital signs/Physical examination

Vital signs (i.e., systolic blood pressure, diastolic blood pressure and pulse rate) will be summarized at each timepoint as well as absolute changes from baseline.

6.4.6. Other safety parameters

Pregnancy

Considering female patients, at screening a serum pregnancy test should be performed for all women of childbearing potential. The proportion of patients who perform the pregnancy test together with the corresponding results will be provided. For female patients who do not perform pregnancy test the reason will be summarized (i.e., premenarchal, menopause, sterile, other).

Ophthalmic examination:

A complete ophthalmic examination will be performed on the study eye at Screening, Baseline and Week 48 and may be performed at each in-between scheduled visit by the Investigator. At each visit the Investigators have to exclude the presence of any active intraocular inflammation in the study eye. This exam is also to be performed on the fellow eye at Screening and Week 48. Only data related to study eye will be summarized.

The ophthalmic exam may consist of the following:

- Biomicroscopy (slit lamp examination): the proportion of patients with any abnormal signs in anterior chamber (cells/flare) or Vitreous (cells/haze), the proportion of patients with any signs of Intraocular Inflammation (IOI) will be summarized at each visit. Moreover, the severity of anterior chamber cells and flare and the severity of vitreous cells and haze will be summarized considering the following categories:
  - for *Anterior Chamber cells*: 0 (<1), 0.5+ (1-5), 1+ (6-15), 2+ (16-25), 3+ (26-50), 4+ (>50).
  - for *Anterior Chamber flare*: 0 (None), 1+ (Faint), 2+ (Moderate: iris and lens details clear), 3+ (Marked: iris and lens details hazy), 4+ (Intense: fibrin or plastic aqueous).
  - for *Vitreous cells*: 0 (Clear: None), 0.5+ (Few opacities: 1-10 cells), 1+ (Scattered opacities: 11-20 cells), 2+ (Moderate opacities: 21-30 cells), 3+ (Many opacities: 31-100 cells).
  - for *Vitreous haze*: 0 (No haze), 0.5+ (Sometime subtle), 1+ (Permits a better definition of both optic nerve head and the retinal vessels), 2+ (Permits better visualization of the retinal vessels), 3+ (Optic nerve head is visible, but the borders are quite blurry), 4+ (Optic nerve head is obscured).
- Fundus (posterior segment) analyzed by the Color Fundus Photography (CFP). The Investigator's monitoring the disease activity of patients and in case of clinically significant abnormalities they will be collected and analyzed as adverse events. A description of qualitative parameters measured in the study eye at screening is provided as described in section 5.2 of the present document.
- Intraocular pressure (IOP) measurement will be summarized at each timepoint as well as absolute changes from baseline considering both pre-dose and post-dose assessments of IOP.

6.5. Subgroup Analyses

Not applicable.

6.6. Interim Analysis and Data Monitoring

The interim analysis was planned as per protocol after approximately 50% of enrolled participants have reached Week 16 in the study. Week 16 visit date of last enrolled patient considered for the interim (i.e., approximately the 132nd patient) should be used as cut-off date.

However, the enrolment of patients was closed on October 2022 with 122 enrolled patients, that is lower than the target of 50%.

For this reason, the interim analysis will include all patients enrolled in the study and the Week 16 visit date of last enrolled patient will be used as cut-off date.

The interim analysis was performed considering all enrolled patients and as cut-off date the February 16, 2023. The interim analysis was focused to evaluate the reasons underlying the Investigator's choice of brolucizumab treatment regimen at week 16, q12w or q8w, therefore determinants in Investigator's choice of dosing regimen will be taken into account. Considered determinants are:

- Best-corrected visual acuity (BCVA);
- Leakage at FA/ICGA;
- Central Subfield Thickness (CST) at SD-OCT;
- Intraretinal Fluid (IRF) at SD-OCT;
- Subretinal Fluid (SRF) at SD-OCT;
- Sub-Retinal Pigment Epithelium (sub-RPE) fluid at SD-OCT;
- Retina Pigment Epithelial Detachment volume at SD-OCT;
- Central Retinal Thickness (CRT);
- Subretinal hyperreflective material (SHRM) at SD-OCT;
- CNV size at OCTA;
- Vessel density at OCTA;
- Vessel morphology at OCTA;
- Hemorrhage at CFP.

Demographic data, medical history, vital signs, ophthalmic examination, history of primary diagnosis, anatomical ocular parameters (i.e., CFP, FA, SD-OCT, OCTA, BCVA), disease activity at week 16 will be summarized and described. Safety data focused on the incidence of ocular and non-ocular adverse events will also be summarized.

7. REFERENCES

Not applicable.

8. APPENDIX

Not applicable.

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Envelope Originator:
Certificate Pages: 5
Initials: 0
[redacted]
AutoNav: Enabled
[redacted]
EnvelopeId Stamping: Enabled
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Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna
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Record Tracking

Status: Original
28-Nov-2023 | 17:29
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 91ECB3EA-C193-4E10-B278-E0B3DF2F851E Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 28-Nov-2023 | 17:31 Viewed: 28-Nov-2023 | 17:44 Signed: 28-Nov-2023 | 17:45
Electronic Record and Signature Disclosure: Accepted: 03-Oct-2023 | 17:32 ID: faef3bbf-d8d6-457e-ac2c-c1f8ac869978		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: CAB184AC-49C7-464A-9A87-8EC2EF515A7C Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 28-Nov-2023 | 17:45 Viewed: 28-Nov-2023 | 17:49 Signed: 28-Nov-2023 | 17:50
Electronic Record and Signature Disclosure: Accepted: 03-Oct-2023 | 16:13 ID: 1db8be43-fa96-457c-838a-fcb9ab0512a8		

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: A21F9D1A-EED2-465D-9574-6592E9B988B6 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 28-Nov-2023 | 17:50 Viewed: 28-Nov-2023 | 18:00 Signed: 28-Nov-2023 | 18:01
Electronic Record and Signature Disclosure: Accepted: 28-Nov-2023 | 18:00 ID: ffeda169-77c1-4498-8115-a43e3f7833a5		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	28-Nov-2023 | 17:31
Certified Delivered	Security Checked	28-Nov-2023 | 18:00
Signing Complete	Security Checked	28-Nov-2023 | 18:01
Completed	Security Checked	28-Nov-2023 | 18:01

Payment Events	Status	Timestamps
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