Official Title: A Real-world, Prospective, Multi-center, Open-label, Phase IV Clinical Study to Evaluate Evaluate the Safety and Effectiveness of Intravitreal Injections (IVI) of Brolucizumab in Patients With Neovascular Age-related Macular Degeneration (nAMD)

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Interventional Study Protocol (PASS)

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A real-world, prospective, multi-center, open-label, phase IV clinical study to evaluate the safety and effectiveness of intravitreal injections (IVI) of brolucizumab in patients with neovascular age-related macular degeneration (nAMD)

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List of abbreviations

AE	Adverse Event
AMD	Age-related Macular Degeneration
ANOVA	Analysis Of Variance
ATC	Anatomical Therapeutic Chemical
ATE	Arterial Thromboembolic Events
BCVA	Best Corrected Visual Acuity
BL	Baseline
CI	Confidence Interval
CNV	Choroidal Neo Vascularization
CRF	Case Report/Record Form
CRO	Contract Research Organization
CST	Central Subfield Thickness
DBP	Diastolic Blood Pressure
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report/Record Form
EMA	European Medicines Agency
FA	Fluorescein Angiography
FAS	Full Analysis Set
GCP	Good Clinical Practice
HA	Health Authorities
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IN	Investigator Notification
IOP	Intra-ocular Pressure
IRB	Institutional Review Board
IVI	Intravitreal Injection
IVT	Intravitreal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities

nAMD	Neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
PI	Prescribing Information
REB	Research Ethics Board
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
scFv	Single-Chain fragment variable
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
USFDA	United States Food and Drug Administration
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR1	Vascular Endothelial Growth Factor Receptor 1
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
WHO	World Health Organization
WHO-DRL	World Health Organization Drug Reference List

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	Dr. [redacted]
	Dr. [redacted]

2 Abstract

A real-world, prospective, multi-center, open-label, phase IV clinical study to evaluate the safety and effectiveness of intravitreal injections (IVI) of brolucizumab in patients with neovascular age-related macular degeneration (nAMD).

Version and date

V 0.2

Name and affiliation of the main authors

Dr. [redacted]

Dr. [redacted]

Novartis Healthcare Private Limited (NHPL, India)

Rationale and background

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people affecting 10%-13% of individuals over the age of 65 in North America, Europe, and Australia (Smith 2001, Rein 2009, Kawasaki 2010). Genetic, environmental, and health factors play an important role in the pathogenesis of the disease.

AMD is classified into two clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form (Ferris 1984, Lim 2012, Miller 2013). Neovascular age-related macular degeneration (nAMD) is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or sub-retinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (Ferris, 1984). These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss (Shah 2007, Shah 2009). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (Blinder 2003). Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments (Ferris 1983, Sommer 1991, Wong 2008).

VEGF has been shown to be elevated in patients with neovascular AMD and is thought to play a key role in the neovascularization process (Spilsbury 2000). The use of intravitreal (IVT) pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with neovascular age-related macular degeneration (Bloch 2012, Campbell 2012). Anti-VEGF

treatments, such as ranibizumab (LUCENTIS) and aflibercept (EYLEA), inhibit VEGF signaling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal edema.

Brolucizumab, formerly known as ESBA1008, is a humanized single-chain Fv (scFv) antibody fragment inhibitor of VEGF with a molecular weight of ~26 kDa that is being developed for the treatment of CNV associated with neovascular AMD. It is an inhibitor of VEGF-A and works by binding to the receptor binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells. Increased levels of signaling through the VEGF pathway are associated with pathologic ocular angiogenesis and retinal edema. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and resolve retinal edema in patients with nAMD (Nguyen 2020, Brolucizumab Prescribing Information).

Two pivotal phase 3 trials (HAWK and HARRIER) with similar designs, compared brolucizumab with aflibercept to treat nAMD in 1817 patients with untreated, active CNV due to AMD in the study eye. Brolucizumab was non-inferior to aflibercept in visual function at Week 48, and more than 50% of brolucizumab 6 mg-treated eyes were maintained on 12 weekly dosing through Week 48. Greater central subfield thickness (CST) reductions from baseline to Week 48 were observed with brolucizumab 6 mg versus aflibercept. Anatomic retinal fluid outcomes favored brolucizumab over aflibercept. Overall, adverse event rates were generally similar with brolucizumab and aflibercept (Dugel 2020).

Currently, the drug is approved by the USFDA, the European Medicines Agency (EMA), and the Drugs Controller General of India (DCGI). This study is being conducted as part of the post-marketing regulatory requirements in India.

The purpose of this study is to generate additional safety and effectiveness data in a larger nAMD patient population in India that more closely resembles the real-world population intended to be treated with brolucizumab.

The final data from this study would be compared descriptively with the corresponding data from Hawk and Harrier (Dugel 2020).

Research question and objectives

Primary Objective:

1. To evaluate ocular & non-ocular safety of intravitreal brolucizumab in real-world patients with nAMD.

Primary Endpoints:

Incidence and characteristics of treatment-emergent adverse events during the 56 weeks of treatment with brolucizumab.

Secondary Objectives:

1. To evaluate the effectiveness of brolucizumab in the management of nAMD in terms of change in best-corrected visual acuity (BCVA) from baseline to Week 56.

2. Characterize the number of anti-VEGF injections, number of non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab.
3. Estimate the percentage (%) of patient eyes with anti-VEGF injection intervals q8w and q12w during the 56 weeks of treatment with brolucizumab.
4. Estimate effect of brolucizumab on fluid from baseline to week 16 and week 56.
5. Estimate effect of brolucizumab on central subfield thickness (CST) from baseline to week 16 and week 56.

Secondary Endpoints

1.1 Mean change in BCVA from baseline to week 16 and week 56 as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

1.2 Percentage (%) of patient eyes with gain in BCVA of 15/10/5 ETDRS letters or more from baseline to week 16 and week 56.

1.3 Percentage (%) of patient eyes with loss in BCVA of 15/10/5 ETDRS letters or more from baseline to week 16 and week 56.

2. Number of anti-VEGF injections, non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab.

3.1 Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 8 weeks but <12 weeks.

3.2 Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 12 weeks.

4.1 Absence of intra-retinal fluid from baseline to week 16 and week 56.

4.2 Absence of sub-retinal fluid from baseline to week 16 and week 56.

5. Estimate CST change from baseline (in µm) to week 16 and at week 56.

Study design

This is a prospective, multi-center, open-label, interventional phase IV clinical study. The study treatment i.e. brolucizumab will be prescribed in terms of the marketing authorization; the assignment of the patient to the therapy will be decided within the current practice and the medical indication, and will clearly be separated from the decision to include the patient in the study.

All patients with nAMD who are planned to be treated with brolucizumab and have provided informed consent may be enrolled in this study. The treatment period for each patient will be 56 weeks after the start of brolucizumab treatment. Study visits will be scheduled at week 4, week 8, week 16, and thereafter at intervals of 8 weeks or 12 weeks after disease activity assessment at week 16. If the investigators require more frequent follow-up visits, it can be done according to their discretion and clinical judgment. Any patient who suffers from intra-ocular inflammation (IOI) during the study period would not be re-challenged with brolucizumab.

Data originating from assessments and evaluations performed will be collected from the patient's medical records at Baseline (BL), i.e. start of brolucizumab treatment, week 4, week 8, week 16, week 20, week 24, week 32, week 40, week 44, week 48 and at week 56.

Setting and study population

The study plans to enroll a total of 105 patients in 10 centers.

Inclusion criteria:

1. Female or male, treatment naïve patient with ≥50 years of age, with neovascular age-related macular degeneration (nAMD).
2. Patient or legally acceptable representative (LAR) willing to voluntarily provide signed informed consent for participation in the study.

Note: In case where both eyes are affected, data of only one eye ['study eye'] will be recorded. selection of the eye to be considered for the purpose of the study [referred to as 'study eye'] will be as per the Investigator's discretion.

Exclusion criteria:

Patients fulfilling any of the following criteria are not eligible for this study:

1. Patient having other eye diseases that could compromise the visual acuity (VA).
2. Patient with existing or suspected ocular or periocular infection in the study eye.
3. Patient with an existing intraocular inflammation (IOI).
4. Patient with uncontrolled glaucoma defined as intraocular pressure > 25 mmHg despite treatment with anti-glaucoma medication, or according to Investigator's judgment.
5. Patient who has undergone intraocular surgery within 3 months prior to enrollment in this study
6. Patient having scar, fibrosis and atrophy involving the center of the fovea in the study eye.

Variables

- Demographic and baseline characteristics
- Physical examination
- Vital signs
- Effectiveness variables
    - Visual acuity (VA)
    - Number of brolucizumab injections for treatment during the study duration
    - q8w and q12w injection interval
    - Intra-retinal fluid (IRF) and Sub-retinal fluid (SRF)
    - Central subfield thickness (CST)
- Safety variables
    - Adverse events (AEs) and serious adverse events (SAEs) reporting
    - any significant changes in the vital signs and/or physical examination parameters

Data sources

Information on brolucizumab administration since treatment start will be recorded in the Case Report/Case Record Form (CRF). All concomitant medications including the reason for prescribing the medication and the start and end dates will be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Initiation of the participating sites will be performed by Novartis and/or a designated Contract Research Organization (CRO).

Sites enrolling subjects in this study will record data on eCRFs provided by Novartis. A designated CRO will capture, check, store and analyze the data.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the MedDRA terminology.

Study size

The sample size of this interventional study will be 105 considering 10% dropouts/lost to follow-up. The actual estimated sample size is 95.

Data analysis

All analyses will be performed by Novartis and/or a designated CRO after all enrolled patients complete the 56 weeks study period.

Milestones

Planned dates of study milestones:

Primary data collection for this interventional study will be as mentioned below:

Planned protocol finalization date: 6th May 2021

Planned start of data collection (FPFV): 01 May 2022

Planned end of data collection (LPLV): 01 Dec 2023

Interim safety report: Quarterly

Planned Interventional study Report date (interim/final report): 01 June 2024

Planned first publication date: 01 Jul 2025

3 Amendments and updates

None

4 Milestones

Table 4-1 Planned date of study milestones

Milestone	Planned date
Start of data collection	01 May 2022
End of data collection	01 Dec 2023
Interim safety report	Quarterly
Final report of study results	01 June 2024

5 Rationale and background

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people affecting 10%-13% of individuals over the age of 65 in North America, Europe, and Australia [1-3]. Genetic, environmental, and health factors play an important role in the pathogenesis of the disease.

Neovascular AMD is classified into two clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form [4-6]. Neovascular age-related macular degeneration (nAMD) is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or sub-retinal space from the subjacent choroid, termed choroidal neovascularization (CNV) [5]. These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss [7, 8]. Without treatment, most affected eyes will have poor central vision (20/200) within 12 months [9]. Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments [5, 10, 11].

VEGF has been shown to be elevated in patients with neovascular AMD and is thought to play a key role in the neovascularization process [12]. The use of intravitreal (IVT) pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with neovascular age-related macular degeneration [13,14]. Anti-VEGF treatments, such as ranibizumab and aflibercept inhibit VEGF signaling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal edema.

Brolucizumab, formerly known as ESBA1008, is a humanized single-chain Fv (scFv) antibody fragment inhibitor of VEGF with a molecular weight of ~26 kDa that is being developed for the treatment of CNV associated with nAMD. It is an inhibitor of VEGF-A and works by binding to the receptor binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells.

Increased levels of signaling through the VEGF pathway are associated with pathologic ocular angiogenesis and retinal edema. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and resolve retinal edema in patients with nAMD. There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors [15,16].

Two pivotal phase 3 trials (HAWK and HARRIER) with similar designs, compared brolucizumab with aflibercept to treat nAMD in 1817 patients with untreated, active CNV due to AMD in the study eye. Brolucizumab was non-inferior to aflibercept in visual function at Week 48:each brolucizumab arm demonstrated non inferiority to aflibercept in best-corrected visual acuity (BCVA) change from baseline (least squares [LS] mean, +6.6 [6 mg] and +6.1 [3 mg] letters with brolucizumab vs. +6.8 letters with aflibercept [HAWK]; +6.9 [brolucizumab 6 mg] vs. +7.6 [aflibercept] letters [HARRIER]; $P < 0.001$ for each comparison). Greater than 50% of brolucizumab 6 mg-treated eyes were maintained on q12w dosing through Week 48 (56% [HAWK] and 51% [HARRIER]). At Week 16, after identical treatment exposure, fewer brolucizumab 6 mg-treated eyes had disease activity versus aflibercept in HAWK (24.0% vs. 34.5%; $P = 0.001$) and HARRIER (22.7% vs. 32.2%; $P = 0.002$). Greater central subfield thickness reductions from baseline to Week 48 were observed with brolucizumab 6 mg versus aflibercept in HAWK (LS mean -172.8 µm vs. -143.7 µm; $P = 0.001$) and HARRIER (LS mean -193.8 µm vs. -143.9 µm; $P < 0.001$). Anatomic retinal fluid outcomes favored brolucizumab over aflibercept. Overall, adverse event rates were generally similar with brolucizumab and aflibercept [17].

Currently, brolucizumab is approved by the USFDA, the European Medicines Agency (EMA), and the Drugs Controller General of India (DCGI). This multi-center, open-label, prospective, interventional, phase IV study is being conducted as part of the post-marketing regulatory requirements in India.

This study will evaluate the safety and effectiveness of intravitreal injections (IVI) of brolucizumab in patients with neovascular age-related macular degeneration (nAMD) over 56 weeks.

The purpose of this study is to generate additional safety and effectiveness data in a larger nAMD patient population in India that more closely resembles the real-world population intended to be treated with brolucizumab.

It is expected that this study will provide the real-world determinants of clinical response to brolucizumab. The final data of this study would be compared descriptively with the corresponding data from the Hawk and Harrier studies [17].

6 Research question and objectives

The purpose of this study is to generate additional safety and effectiveness data in Indian nAMD patients that more closely resemble the real-world population intended to be treated with brolucizumab.

This study is being conducted as part of the post-marketing regulatory commitment to the Indian Health authority.

6.1 Primary Objective

1. To evaluate ocular & non-ocular safety of intravitreal brolucizumab in real-world patients with nAMD.

6.2 Secondary Objectives

1. To evaluate the effectiveness of brolucizumab in the management of nAMD in terms of change in best-corrected visual acuity (BCVA) from baseline to Week 56.
2. Characterize the number of anti-VEGF injections, number of non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab.
3. Estimate the percentage (%) of patient eyes with anti-VEGF injection intervals q8w and q12w during the 56 weeks of treatment with brolucizumab.
4. Estimate effect of brolucizumab on fluid from baseline to week 16 and week 56.
5. Estimate effect of brolucizumab on central subfield thickness (CST) from baseline to week 16 and week 56.

7 Research methods

7.1 Study design

This is a prospective, multi-center, open-label, interventional phase IV clinical study. The study treatment i.e. brolucizumab will be prescribed in terms of the marketing authorization; the assignment of the patient to the therapy will be decided within the current practice and the medical indication, and will clearly be separated from the decision to include the patient in the study.

All patients with nAMD who are planned to be treated with brolucizumab and have provided informed consent may be enrolled in this study. The treatment period for each patient will be 56 weeks after the start of brolucizumab treatment. Study visits will be scheduled at week 4, week 8, week 16, and thereafter at intervals of 8 weeks or 12 weeks after disease activity assessment at week 16. If the investigators require more frequent follow-up visits, it can be done according to their discretion and clinical judgment. The study drug will be provided free of cost to the patients in the study. Any patient who suffers from intra-ocular inflammation (IOI) during the study period would not be re-challenged with brolucizumab.

Data originating from assessments and evaluations performed will be collected from the patient's medical records at Baseline (BL), i.e. start of brolucizumab treatment, week 4, week 8, week 16, week 20, week 24, week 32, week 40, week 44, week 48 and at week 56.

7.1.1 Primary Endpoint

Incidence and characteristics of treatment-emergent adverse events during the 56 weeks of treatment with brolucizumab.

7.1.2 Secondary Endpoints

1.1 Mean change in BCVA from baseline to week 16 and week 56 as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

1.2 Percentage (%) of patient eyes with gain in BCVA of 15/10/5 ETDRS letters or more from baseline to week 16 and week 56.

1.3 Percentage (%) of patient eyes with loss in BCVA of 15/10/5 ETDRS letters or more from baseline to week 16 and week 56.

2. Number of anti-VEGF injections, non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab.

3.1 Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 8 weeks but <12 weeks.

3.2 Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 12 weeks.

4.1 Absence of intra-retinal fluid from baseline to week 16 and week 56.

4.2 Absence of sub-retinal fluid from baseline to week 16 and week 56.

5. Estimate CST change from baseline (in μm) to week 16 and at week 56.

7.2 Setting

The study population will consist of adult male and female outpatients aged 50 years and above, diagnosed with nAMD for whom the treating physician (Investigator) prescribes treatment with brolucizumab 6 mg injection in adherence with the local Summary of Product Characteristics (SmPC) or Prescribing Information (PI). The treatment with brolucizumab should not have been be prescribed for the purpose of entering a patient in this interventional study, but solely based on the clinical judgment of the treating physician. Patients will be considered eligible for this study only after the decision to prescribe brolucizumab has been made as per the treating physician's clinical judgement. The patients should have provided voluntary informed consent to participate in the study.

Brolucizumab 6 mg will be administered by IVT injection as per the Prescribing information (PI) and in line with the treating physician's clinical judgement. Patients will receive loading doses of brolucizumab at Day 0/Visit 1, Week 4/Visit 2 and Week 8/Visit 3. After the loading doses, at Week 16, disease activity assessment (DAA) will be performed based on BCVA and OCT to assess whether the patient will require q8w or q12w dosing.

Patients who are scheduled for q8w dosing with brolucizumab will receive injections at weeks 16, 24, 32, 40, 48.

Patients who are scheduled for q12w dosing of brolucizumab will receive injections at weeks 20, 32, and 44.

DAA will be conducted as per the q8w and q12w dosing administration. Allocation and re-allocation to q8w/q12w dosing regimen will be as per Investigator's discretion.

7.2.1 Inclusion criteria

1. Female or male, treatment naïve patient with ≥50 years of age, with neovascular age-related macular degeneration (nAMD).
2. Patient or legally acceptable representative (LAR) willing to voluntarily provide signed informed consent for participation in the study.

Note: In case where both eyes are affected, data of only one eye ['study eye'] will be recorded. Selection of the eye to be considered for the purpose of the study [referred to as 'study eye'] will be as per the Investigator's discretion.

7.2.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for this study:

1. Patient having other eye diseases that could compromise the VA.
2. Patient with existing or suspected ocular or periocular infection in the study eye.
3. Patient with an existing intraocular inflammation (IOI).
4. Patient with uncontrolled glaucoma defined as intraocular pressure > 25 mmHg despite treatment with anti-glaucoma medication, or according to Investigator's judgment.
5. Patient who has undergone intraocular surgery within 3 months prior to enrollment in this study.
6. Patient having scar, fibrosis and atrophy involving the center of the fovea in the study eye.

7.3 Variables

7.3.1 Demography and Baseline characteristics

Patient demographics, medical history will be done at the first visit at the time of screening (

Table 7-1). Patient demographic and baseline characteristic data taken at study entry will include: date of birth, gender, race, ethnicity, weight and height, smoking history, history of ocular disease (diagnosis of nAMD and any other ocular conditions), other relevant medical histories (significant medical conditions and surgical events), treatment for nAMD received in the 12 months prior to study entry.

Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term according to the WHO-DRL dictionary.

7.3.2 Physical examination

The physical exam will consist of a routine evaluation of organ systems e.g., ears, eyes, nose, throat, neck, lymph nodes, lungs, heart, abdomen, skin/extremities, neurological, and musculoskeletal systems.

Information for all physical examinations will be included in the source documentation at the study site. Clinically relevant findings that are present prior to initiating treatment with brolucizumab 6 mg injection must be included in the appropriate section of the CRF.

7.3.3 Vital signs

Vital signs including blood pressure (BP), heart rate, systolic (SBP) and diastolic blood pressure (DBP) will be measured when the patient has been sitting for approximately five minutes. If an automated blood pressure device is used, it should be calibrated according to the manufacturer's guidelines.

7.3.4 Effectiveness variables

1. Visual acuity (VA) in ETDRS letter
2. Number of brolucizumab injections for treatment during study duration
3. q8w and q12w injection interval
4. Intra-retinal fluid (IRF) and Sub-retinal fluid (SRF)
5. Central subfield thickness (CST)

7.3.5 Safety variables

Adverse events (AEs) and serious adverse events (SAEs) reporting

Treatment-emergent changes in any of the ocular parameters, which meet the definition of an Adverse Event (serious and non-serious), will be recorded in the appropriate section of the CRF.

Any significant changes in the vital signs and/or physical examination parameters observed after first administration of brolucizumab which meet the definition of an Adverse Event will be recorded in the appropriate section of the CRF.

Exposure of interest

Exposure to study medication from start to end of treatment within this interventional study. The number (%) of patients who discontinue prematurely prior to 56 weeks with including the

reasons for discontinuation. Furthermore, the number of injections will be presented for the total study period.

7.3.6 Data sources

Information on brolucizumab administration since treatment start will be recorded in the Case Report/Case Record Form (CRF). All concomitant medications including the reason for prescribing the medication and the start and end dates will be recorded on the concomitant medications/significant non-drug therapies CRF.

Initiation of the participating sites will be performed by Novartis and/or a designated Contract Research Organization (CRO).

Sites enrolling subjects in this study will record data on eCRFs provided by Novartis. A designated CRO will capture, check, store and analyze the data.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the MedDRA terminology.

7.3.7 Data collection schedule

Data originating from routine patient visits and assessments at study time points (Baseline, i.e. start of brolucizumab treatment, and approximately week 4, week 8, week 16, week 20, week 24, week 32, week 40, week 44, week 48 and at week 56 post-initiation of treatment/or discontinuation of treatment) and safety data (AEs and SAEs, see Section 8) from any time point during the duration of the study will be recorded for the purpose of this study. Data will be collected only on the eye treated with brolucizumab and if both eyes are treated with brolucizumab, the data from one eye (study eye) will be recorded. The selection of eye (study eye) will be as per discretion of the Investigator at the time of enrolment in this study.

Participation in this prospective interventional study and confirmation of patient consent to collect and use patient data will be documented using an informed consent form by the site staff on or before the baseline visit. A copy of this signed document will be given to the patient and the original will remain in the patient's records.

Each patient is uniquely identified in the study by a combination of the Investigator's center number and a patient number. The center number is assigned by Novartis (or designee), the patient number is assigned by the Investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2; the third patient is assigned patient number 3, and so forth). Once assigned to a patient, the patient number will not be reused.

Table 7-1 Data collection

Visit number	1	2	3	4	5	6	7	8	9	10	11
Time of visit [Week (Wk)]	Wk 0	Wk 4±1	Wk 8±1	Wk 16±1	Wk 20±1	Wk 24±1	Wk 32±1	Wk 40±1	Wk 44±1	Wk 48±1	Wk 56 (Follow-up) EOS
Inclusion/ Exclusion Criteria	X										
Informed consent	X										
Demographics and Baseline Characteristics	X										
Physical Examination	X										
Vital Signs	X										
Brolucizumab	X	X	X	X*	X#	X*	X*#	X*	X#	X*	
BCVA	X	X	X	X*#	X#	X*	X*#	X*	X#	X*	X
IOP	X	X	X	X*#	X#	X*	X*#	X*	X#	X*	X
Fundus photography	X			X*#			X*#				X
OCT	X	X	X	X*#	X#	X*	X*#	X*	X#	X*	X
Fluorescein Angiography (FA)	X										X
Adverse Events	X	X	X	X*#	X#	X*	X*#	X*	X#	X*	X

* - q8w dosing

- q12w dosing

Note: If the patient comes up at an unscheduled visit or more frequently, his/her BCVA should be measured as for the other visits.

7.4 Study size

The sample size of this interventional study is based on statistical consideration. The current study proposes to recruit 105 patients.

For calculating sample size, safety results of the Phase 3 studies (Dugel 2020) were used. From these studies, the adverse event rate for relevant adverse events is assumed to be approximately 1/100.

The sample size was estimated empirically using 1000 replicates for each sample size between 10 and 250 participants. The number of patients was selected to ensure at least a 90% probability that at least one of these rare adverse events will be observed in the study, which will allow the development of a comprehensive safety profile within the Indian population specifically.

Estimated sample size: N = 95

Additional 10% sample required for patient attrition over 56 weeks (dropouts/lost to follow-up).

Total sample size required: N = 105

7.5 Data management

7.5.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRFs using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated Investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated Investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock or when a site is closed, the Investigator will archive the copies of the patient data at the investigational site.

The Principal Investigator is responsible for assuring that the data entered by the site personnel into the CRF is complete, accurate, and that entry and updates are performed in a timely manner.

7.5.2 Database management and quality control

Novartis personnel or designated CRO personnel will review the data entered by study site staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator/site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List (WHO_DRL), which employs the ATC classification system.

Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis.

7.6 Data analysis

All analyses will be performed by Novartis or a designated CRO.

An interim safety analysis will be performed for the first 50 patients and a quarterly interim safety report will be submitted to the Indian Regulatory Authority, as per their requirements. A complete analysis will be done after all enrolled patients complete the 56 weeks study period or discontinue the study prior to week 56.

7.6.1 General statistical considerations

Summary statistics for continuous variables will include the number of observations (n), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum. Categorical variables will be presented with absolute and relative frequencies. In addition, key results will be presented with two-sided 95% confidence intervals and p-values for within-subject changes across time.

If no post-baseline value is available for a parameter, then the patient will be removed from the analysis of this parameter. Otherwise, if at least one post-baseline value is available, missing values will be imputed by the last observation carried forward (LOCF) principle regardless of the reason for missing data. Apart from specific summaries and analyses described below, all CRF data will be listed.

7.6.2 Analysis sets

The Full Analysis Set (FAS) will consist of all patients who provided informed consent and are treated with brolucizumab in this interventional study. All effectiveness and safety analyses will use the FAS population.

7.6.3 Patient demography and other baseline characteristics

Demographics and other baseline characteristics will be collected at the first visit prior to the start of brolucizumab treatment. Descriptive statistics (as described under section 7.6.1 “General statistical considerations” above) will be presented for continuous variables.

The following variables will be summarized with descriptive statistics as outlined above: age, gender and baseline values of BCVA, baseline risk factors and ocular related history, and vital signs.

Furthermore, the number (%) of patients will be summarized for prior nAMD treatments by WHO-DRL preferred term, for relevant medical histories by MedDRA primary system organ class and preferred term, and for other ocular conditions by type of condition.

7.6.4 Treatments

A data listing of the study drug (brolucizumab) received by the patient will be provided, and the proportion of participants receiving treatment will be summarized by visit. Exposure to study medication will be summarized by the duration (in days) from start to end of treatment within this interventional study. The number (%) of patients who discontinue prematurely prior to 56 weeks will be tabulated including the reasons for discontinuation. Furthermore, the number of injections will be presented for the total study period.

In addition, the number and percentage of participants receiving rescue medications, concomitant medications, and significant non-drug therapy will be summarized by preferred term (coded by WHO ATC classification) and the same shall be listed.

7.6.5 Safety and Effectiveness analysis

Primary Endpoint Analysis

- Incidence and characteristics of treatment-emergent adverse events during the 56 weeks of treatment with brolucizumab would be evaluated.

Safety of brolucizumab treatment will be assessed by reported (ocular and systemic) adverse events (AEs). The incidence of AEs (new or worsened after the start of brolucizumab) will be summarized by MedDRA primary system organ class and preferred term. Similar summaries will be provided for fatal AEs and other serious AEs, AEs causing discontinuation of study drug, and AEs suspected to be related to the study medication (as assessed by the Investigator). Furthermore, AEs will be summarized by primary system organ class, preferred term and severity. Incidence rates will also be determined per treatment year, both for the first occurrence of an event and total events. An adverse event management protocol/mitigation plan would be provided to all the investigators to manage an event of intra-ocular inflammation.

Secondary Endpoints Analysis

The secondary endpoints will evaluate the effectiveness of brolucizumab in terms of change in the following parameters from Baseline to the end of week 56. BCVA at baseline, week 16 and 56 including the change will be summarized with standard descriptive statistics.

- Mean change in BCVA from baseline to week 16 and week 56 as measured by ETDRS letters.
- Percentage (%) of patient eyes with gain in BCVA of 15/10/5 ETDRS letters or more at week 16 and week 56
- Percentage (%) of patient eyes with loss in BCVA of 15/10/5 ETDRS letters or more at week 16 and week 56.
- Number of anti-VEGF injections, non-injection visits and total number of visits
- Percentage (%) of patient eyes with at least one duration of interval between injections $\geq$ 8 weeks but <12 weeks.
- Percentage (%) of patient eyes with at least one duration of interval between injections $\geq$ 12 weeks.

- Percentage of patients with absence of intra-retinal fluid from baseline to week 16 and week 56.
- Percentage of patients with absence of sub-retinal fluid from baseline to week 16 and week 56.
- Estimated change in CST (in µm) from baseline to week 16 and week 56.

7.7 Quality control

7.7.1 Data quality management

Novartis Data Management or/designated CRO will assure database quality processes are followed including review of the data entered into the eCRFs by investigational site staff for completeness and accuracy, and in accordance with the data validation plan.

7.7.2 Data recording and document retention

In all scenarios, the Investigator must maintain source documents for each patient in the study, consisting of the case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file.

The Investigator must give Novartis (or designee CRO) access to all relevant source documents to confirm their consistency with the eCRF entries. No information in source documents about the identity of the patients will be disclosed.

The Investigator will retain a copy of all source documents and study records in accordance with the local regulations. The Investigator is recommended to contact Novartis before disposing off any study records.

7.7.3 Site monitoring

The monitors appointed by the CRO/Novartis, or Novartis designee will perform all monitoring functions within this clinical study. Monitors will work in accordance with Standard Operating Procedures (SOPs) of Novartis or the CRO, as designated in the contract. Monitors will be responsible for establishing and maintaining regular contact between the Investigator and Novartis. Monitors will also control adherence to the protocol at the Investigator site.

Monitors will evaluate the competence of each study center. Monitors will inform Novartis regarding problems relating to facilities, technical equipment, or medical staff. Monitors will ensure that written informed consent has been correctly obtained from all patients and during the study will ensure that data are recorded correctly and completely.

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

Novartis Data Management/designated CRO will ensure compliance monitoring.

7.8 Limitations of the research methods

Limitations of Phase IV studies include the potential for observer bias due to lack of blinding and the absence of standardized data collection, and the potential for selection bias due to lack of randomization. However, this is a single-arm, open-label study and the patients would be eligible for this study only after the Investigator makes a decision to prescribe intravitreal brolucizumab.

7.9 Other aspects

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her wellbeing. All data generated up to the time of discontinuation from the study will be analyzed and the reason(s) for discontinuation/withdrawal will be recorded.

Patients must be discontinued from the study in the case of:

- Withdrawal of informed consent to collect or use their data
- Significant safety risk
- The Investigator must record the discontinuation/withdrawal reason in the Case Record Form (CRF). Reasons that a patient discontinues treatment and participation from the study are considered to constitute one of the following:
- Adverse event(s)
- Unsatisfactory therapeutic effect
- Subject's condition no longer requires study treatment
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death

Patients who discontinue brolucizumab treatment should be asked to return for an early discontinuation assessment. For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by contacting the patients and asking them to return for a final assessment. Every effort should be made to obtain the reason for discontinuation.

The Investigator should document in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

For the purpose of this study, the study drug brolucizumab will be provided free of costs for the patients in this study.

8 Protection of human subjects

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC/REB before the study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a Regulatory Authority, the Investigator must inform Novartis immediately that this request has been made.

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB, it cannot be implemented.

8.1 Regulatory and ethical compliance

This clinical study is designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (New Drugs and Clinical Trial Rules, 2019 of the Drugs and Cosmetics Act, 1945 (Govt. of India), US CFR 21, and with the ethical principles laid down in the Declaration of Helsinki. The study protocol and related information will be posted on India's clinical trial registry – ctri.nic.in – before patient enrolment is started.

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

Written notification of approval for the study must also be obtained from an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to commencement of the study and will include the date of approval and signature of the chairman/member secretary.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of patients or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IEC/IRB annually, or more frequently if requested by the IEC/IRB. Upon completion of the study, the Investigator will provide the IEC/IRB with a brief report of the outcome of the study, if required.

8.2 Informed consent procedures

The Investigator must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative (LAR) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of giving consent, he/she should personally sign and date the written informed consent. If the patient or LAR cannot read, then an impartial witness (independent of Novartis and Investigator) will witness and attest the entire consent process and will be required to sign the ICF. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient's source documents.

Novartis will provide Investigators or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

8.3 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/Institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, documented informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and Regulatory Authorities as required. If an inspection of the clinical site is requested by a Regulatory Authority, the Investigator must inform Novartis immediately that this request has been made.

9 Safety Monitoring

Any serious adverse events will be reported to the concerned Ethics Committee within 24 hours of the occurrence. All serious adverse events will also be reported to Novartis Patient Safety within 24 hours of the Investigator (or designee) being aware of the serious adverse event. Specific definitions of adverse events, and serious adverse events, are outlined below, along with reporting criteria required by Novartis.

If the COVID-19 pandemic limits or prevents on-site study visits, phone calls or virtual contacts should be conducted for safety monitoring and discussion of the subject´s health status, until

the subject can again visit the site.

9.1 Adverse events (AE)

Information about all AEs, whether volunteered by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on an Adverse Event Case Report Form and will be followed up as appropriate.

An AE is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related. Study treatment includes the study medication under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment will only be considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form will be recorded on the Medical History/Current Medical Conditions Case.

For surveillance/monitoring of signs and symptoms related to Intra-ocular inflammation following initial injections of brolucizumab, the recommendations as mentioned below need to be followed by the study Investigator:

- After Injecting brolucizumab, inform the patient about the symptoms of intra-ocular inflammation [eye pain, eye redness, blurred/decreased vision, dark, floating spots in the vision (floaters), light sensitivity, flashes, scotoma (blind spot in vision)].
- And inform the patient to report immediately if he/she sees/experiences any of the signs/symptoms as mentioned above.
- When IOI, retinal vasculitis, and/or RAO is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps).
- These additional assessments will be documented in the source and appropriate eCRF pages as applicable.
- Follow-up the patient in the first week after injection to look for/assess symptoms (Phone call/Visit).
- An adverse event management protocol/mitigation plan would be provided to all the investigators to manage an event of intra-ocular inflammation.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. the severity grade (mild, moderate, severe);
2. its relationship to the drug(s) of interest (suspected/not suspected);
3. its duration (start and end dates or if continuing at final exam); and
4. whether it constitutes a serious adverse event (SAE);

9.2 Serious Adverse Events (SAEs)

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event will also be reported to Novartis Patient Safety within 24 hours of the Investigator learning of its occurrence.

An SAE is defined as an event which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes);
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest; or
    - social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Transmission of an infectious agent via medicinal product

Any SAEs exempt from this reporting process must be clearly identified in the study protocol with a scientific/medical justification e.g. SAEs due to disease progression, SAEs due to a planned surgical procedure, etc. Any SAE study protocol exemptions MUST be agreed with the respective country health authority as part of the protocol approval process. This confirmation by the HA must be recorded and kept on file for the study concerned.

Any SAE occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation will be reported. Serious adverse events occurring more than 4 weeks after study discontinuation will be reported to Novartis Patient Safety only if a relationship with the study therapy is suspected by the Investigator.

As far as possible, each SAE will also be described by (but not limited to):

- its duration (onset date = date of 1st signs or symptoms, and end dates);
- the seriousness criteria and severity if applicable (mild, moderate, severe);
- its relationship to the current investigational drug (suspected/not suspected as judged by the Investigator);
- the action(s) taken and investigation results, if applicable;
- concomitant medication details; and
- outcome.

9.2.1 Notification of serious adverse events to Novartis Pharmaceuticals Patient Safety

Each Serious Adverse Event (SAE) will be reported by the Investigator to Novartis Patient Safety within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported SAE will also be reported to Novartis Patient safety within 24 hours of receiving it. If the SAE has not been previously documented (new occurrence) and it is thought to be related to study treatment, Novartis Patient Safety Department may contact the Investigator to obtain further information.

9.2.2 Reporting procedures

The Investigator will complete the SAE Report Form in English, assess the relationship to study treatment and send the completed and signed form by email within 24 hours to Novartis Patient Safety Novartis Patient Safety will acknowledge the receipt of the full SAE form (all pages) by email back. The original copy of the SAE Form, and the acknowledgement email will be kept with the case report forms at the study site. If the Investigator does not receive an acknowledgement email from Novartis Patient Safety within 24 hours or realize that the number of pages received by Novartis Patient Safety doesn't match the number of pages emailed by the Investigator, the SAE form will be re-sent entirely until Novartis Patient Safety confirms the receipt of the full report.

Follow-up information will be sent to the same person to whom the original SAE Form was sent, re-stating the date of the original report. A new SAE Form will be used (stating that this is a "follow-up"). The follow-up report should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The SAE form and email acknowledgment will be retained by the study site.

To ensure patient safety, each pregnancy in a patient will be reported to Novartis within 24 hours of learning of its occurrence. Pregnancy will be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator to the local Novartis Patient Safety Department. Pregnancy follow-up will be recorded on the same form and will include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy will be reported on the SAE Report Form.

10 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

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