NOVARTIS

Global Medical Affairs

Non-Interventional Study Protocol (PASS) with secondary use of data

CRTH258A2404

Title	Retrospective analysis of imaging and clinical features from patients treated with Brolucizumab in post-marketing setting with reports of intraocular inflammation and/or retinal vascular occlusion
Protocol version identifier	v01
Date of last version of protocol	31-March-2021
EU PAS register number	
Medicinal product	Brolucizumab
Name of Marketing authorization holder(s)	
Joint PASS	Yes
Research question and objectives	This study provides real-world overview of the images collected at time of event of adverse events (AEs) of interest. The primary objective is to characterize the AEs of interest in terms of independent case classification based on imaging data.
Country (-ies) of study	Global
Authors	[redacted]; Novartis AG

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List of abbreviations

AE	Adverse event
A/C	Anterior chamber
CFP	Color Fundus Photography
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FA	Fluorescein Angiography
FP	Fundus Photography
GPP	Good Pharmacoepidemiology Practices
ICGA	Indocyanine Green Angiography
ICMJE	International Committee of Medical Journal Editors
IOI	Intraocular inflammation
ISPE	International Society for Pharmacoepidemiology
nAMD	Neovascular (wet) age-related macular degeneration
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
OD	Oculus dexter (right eye)
OS	Oculus sinister (left eye)
PV	Pharmacovigilance
RV	Retinal vasculitis
RO	Retinal vascular/vein occlusion
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TFU	Targeted follow up
UNG/P	Ungradable picture
UNG/Q	Ungradable quality
US	United States
VA	Visual acuity

1 Responsible parties

Table 1-1 Responsible parties

Role	[redacted], MD [redacted] Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, NJ 07936-1080
Main protocol authors	[redacted]
Principal investigator (PI)	NA
MAH contact person	[redacted]

2 Abstract

Title

Retrospective analysis of imaging features from patients treated with brolucizumab in post-marketing setting with reports of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion

Version and date

v01

Name and affiliation of main author

[redacted], MD
Novartis Pharmaceuticals Corporation

Rationale and background

Brolucizumab has been approved in the United States (US), Europe, Japan, and other countries for the treatment of neovascular (wet) age-related macular degeneration (nAMD).[1-6] Events of occlusive vasculitis have been reported with the use of brolucizumab in the post-marketing setting and a safety signal of "retinal vasculitis (RV) and/or retinal vascular occlusion (RO) with or without presence of intraocular inflammation (IOI) that may result in severe vision loss" has been confirmed.[7-9]

Novartis has developed an enhanced pharmacovigilance (PV) program to enable better characterization of the aforementioned adverse events (AEs) also referred to as AEs of interest reported in the post-marketing setting with brolucizumab use.[10] The enhanced PV program included the collection of ocular images for a limited period of time and review by an external reading center, according to a standardized list of parameters. A summary report of findings will be provided for each case, including an overall imaging-based case classification. The assessment of location and extent of the event, as well as the pathological features on the images will be also provided per case.

The purpose of this retrospective study analysis will be to better characterize the risk of inflammatory events arising from use of brolucizumab in routine clinical practice through analysis of independently reviewed ocular imaging data obtained from cases with reports of IOI, RV and/or RO and to provide a description of these features.

Research question and objectives

This study provides real-world overview of the images collected at time the AEs of interest will be reported to the safety department.

Primary objective

To characterize the AEs of interest in terms of independent case classification based on imaging data

1. Breakdown of imaging classification of the cases
2. Breakdown on location and findings by imaging modality

Exploratory objective

To describe patient demographics, clinical features, and visual outcomes in cases with imaging signs of IOI, RV, and/or RO to characterize the events of interest.

This exploratory objective will only be analyzed if the primary objective is judged to provide clinically relevant information and based on availability of information in the Novartis Patient Safety database ([redacted]).

A subgroup analysis for patients [redacted] will be performed.

Methods

Study design

This is a non-interventional descriptive study related to the enhanced pharmacovigilance program put in place for brolucizumab to better understand the nature of the RV and/or RO with or without inflammation and with or without vision loss.

Whenever an AE report pertaining to RV and/or RO or IOI will be reported to Novartis Patient Safety, a follow-up check list will be sent by Novartis to the reporter. The reporter will be encouraged to share all available images obtained as part of clinical practice; irrespective of the timing vs. event (i.e., images before, at and after event could be provided).

All images obtained for the cases of interest up to 31 January 2021 will be reviewed in a standardized manner by an external reading center ([redacted]).

For each case, the reading center will provide: 1) An overall classification of the eye based on all provided imaging data acquired at the time of event will be generated. Eye cases will be classified as RV only vs. RO only vs. RV + RO only vs. IOI vs. Not assessable vs. None and 2) For each case, timepoint, and imaging modality, the full case assessment including gradable modality images and any observed pathology will be provided. These grading variables will be entered in the study specific database per modality and visit. For each case and timepoint per imaging modality and visit, only one gradable variable assessment will be completed.

The summary reports and the image assessment forms generated from independent classification based on imaging along with clinical features in the Novartis Patient Safety database [redacted] used in the aggregate analysis.

Setting and study population

All post-marketing cases of IOI, RV and/or RO reported to the Novartis Patient Safety worldwide involving brolucizumab use as per routine clinical practice for which images will be provided to Novartis will be considered for this study.

Variables

The main outcome will be the overall classification by the central reader based on the imaging data as RV only vs. RO only vs. RV+RO only vs. IOI vs. Not assessable vs. None. Table 2-1 provides the operational definition used for these classifications.

Table 2-1 Pathology by image modality – case classification and operational definition

Case classification based on imaging data and operational definition
Features Required for IOI (Case classification based on imaging: There is no RO or RV) • OCT = vitreous hyper-reflective dots • FP = media opacities
Features Required for RV • FP = perivascular sheathing, kyrieleis plaque • FA = vascular leakage • ICG = early choroidal vessel hypercyanescence
Features Required for RO • FP = retinal vessel box-carring • FA = retinal arterial occlusion, retinal vein occlusion, retinal vessel box-carring, retinal ischemia, retinal neovascularization, • ICG = choroidal hypocyanescent areas • OCT = inner retinal layer hyperreflectivity, paracentral acute middle maculopathy • OCT-A = superficial or deep capillary plexus ischemia

FA, fluorescein angiography; FP, fundus photography; ICG, indocyanine green; IOI, intraocular inflammation; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RO, Retinal vascular occlusion; RV, Retinal vasculitis.

- Not assessable: When image quality concerns prevented grading, the cases will be deemed as “Not assessable”.

- None: When there no imaging features of intraocular inflammation, retinal vasculitis and retinal vascular occlusion

Data sources

The data for this study will be retrieved from two data sources: imaging data and the Novartis Patient Safety database ([redacted]) provided by (Novartis AG).

The imaging database will be set up for this study and contains the grading variable for the images provided to the reading center. As mentioned in the rationale section Novartis has developed an enhanced pharmacovigilance (PV) program to enable better characterization of the aforementioned AEs also will be referred to as AEs of interest reported in the post-marketing setting with brolucizumab use.[10] The enhanced PV program included the collection of ocular images for a limited period of time and review by an external reading center, according to a standardized list of parameters. A summary report of findings will be provided for each case, including an overall imaging-based case classification. The assessment of location and extent of the event, as well as the pathological features on the images also will be provided per case.

The Novartis Patient Safety database will be used to retrieve the case classification by reading center and further case information (e.g., patient characteristic, visual acuity).

Data will be linked using the [redacted] case ID.

Data analysis

All analyses will be performed by [redacted].

Data will be analyzed and performed by Novartis using SAS version 9.3 or higher in the Novartis programming environment GPSII.

As described herein, only cases with the event of interest and available images will be sent for independent assessment. Consequently, no incidence rate for events of interest will be derived.

Number of (%) assessable vs. non assessable cases based on imaging data will be summarized among all cases with imaging data sent to the central reviewer.

Anatomical location and sub-location (Retina (further classified as general vs. vascular) vs. Vitreous vs. Choroid vs. Optic nerve), type of occlusion (Central vs. Branch vs. Periphery), anatomical location in relation to macula, location details and extent of involvement will be summarized by case classification based on imaging data.

Data on patient characteristics [redacted], treatment, event outcome and visual loss/outcome distribution will be retrieved from the Novartis Patient Safety database.

No missing data imputation will be performed.

Study size

All cases with the event of interest and available images will be sent for independent assessment. This analysis will be descriptive in nature and all cases in the respective cohort will be included.

Milestones

Planned dates of study milestones:

Planned protocol finalization date: [redacted]
Start of primary data collection: [redacted]

End of primary data collection: [redacted]

Planned date from which data extraction starts: [redacted]

Registration in the EU PAS register>: DD Month YYYY

Final report of study results: [redacted]

Planned first publication date: 30 September 2021

3 Amendments and updates

None

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	DD Month YYYY	Section x	Type here	Type here
2	DD Month YYYY	Section x	Type here	Type here
…	DD Month YYYY	Section x	Type here	Type here

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of data extraction	[redacted]
<Registration in the EU PAS register>	DD Month YYYY
Final report of study results	[redacted]

5 Rationale and background

Brolucizumab has been approved in the US, Europe, Japan, and other countries for the treatment of neovascular (wet) nAMD.[1-6] Events of occlusive vasculitis have been reported with the use of brolucizumab in the post-marketing setting and a safety signal of RV and/or RO with or without presence of IOI that may result in severe vision loss" has been confirmed.[7-9]

Novartis has developed an enhanced PV program to enable better characterization of these aforementioned AEs of special events reported in the post-marketing setting with brolucizumab use.[10] The enhanced PV program included the collection of ocular images and review by an external reading center. Dedicated grading lists were developed for each of the image modalities (i.e., Fluorescein Angiography [FA], Fundus Photography [FP], Indocyanine Green Angiography [ICGA], Optical Coherence Tomography [OCT], and Coherence Tomography Angiography [OCT-A])[11-14] and the images will be read according to this standardized list of parameters. A summary report of findings will be provided for each case, including an overall imaging-based case classification. The assessment of location and extent of the event, as well as the pathological features on the images also will be provided per case.

For each case, the independent imaging-based case classification will be stored in Novartis Patient Safety database ([redacted]). Further specific reading parameters and image features will be stored outside of the Novartis Patient Safety database.

The purpose of this retrospective study analysis will be to better characterize the risk of inflammatory events arising from use of brolucizumab in routine clinical practice through analysis of independently reviewed ocular imaging data obtained from cases with reports of IOI and/or RO.

6 Research question and objectives

This study provides real-world overview of the images collected at time of event of AEs of interest.

Primary objective

To characterize **brolucizumab** AEs of interest in terms of independent case classification based on imaging data

1. Distribution of imaging classification of the cases
2. Distribution of location and findings by imaging modality

Exploratory objective

To describe patient demographics, clinical features, and visual outcomes in cases with imaging signs of RV and/or RO to characterize the events of interest. A subgroup analysis for patients [redacted] will be performed.

This exploratory objective will be analyzed only if the primary objective is judged to provide clinically relevant information and based on availability of information in the Novartis Patient Safety database ([redacted]).

Images obtained using any of the following modalities will be considered: FA, FP, ICGA, OCT, and OCT-A.

7 Research methods

7.1 Study design

This is a non-interventional case descriptive study to better understand the nature of the RV and/or RO with or without inflammation and with or without vision loss reported with the use of broclucizumab.

Data collection via rapid response teams will be done for all reported cases of IOI, RV and/or RO. The information will be collected in structured forms (targeted follow up checklists – TFUs) at pre-defined points from when a case with an event of interest will be reported to Novartis.

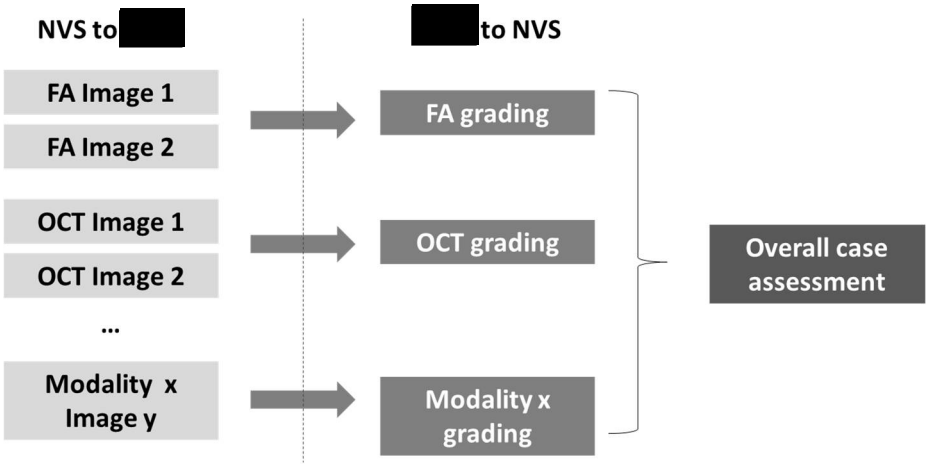
Whenever an AE of RV and/or a RO or IOI will be reported to Novartis Patient Safety, a follow-up check list will be sent by Novartis to the reporter. The reporter will be encouraged to share all available images obtained as part of clinical practice; irrespective of the timing vs. event (i.e., images before, at and after event could be provided).

No restriction will be made in term of type of images collected or method of capture (i.e., any image acquired could be shared such as Color Fundus Photography [CFP] and FA, Spectral Domain Optical Coherence Tomography [SD-OCT], Optical OCT-A, and ICGA). All images obtained for the cases of interest up to 31 January 2021 will be reviewed in a standardized manner by an external reading center ([redacted]).

For each case, the reading center will provide the information as illustrated in (see Figure 7-1): An overall independent overall class classification of the eye based on all provided imaging data (RV only vs. RO only vs. RV + RO only vs. IOI vs. Not assessable vs. None) acquired at the time of event and entered in the Novartis patient Safety database. When image quality concerns prevented grading, the cases will be deemed as “Not assessable”. When there no imaging features of intraocular inflammation, retinal vasculitis and retinal vascular occlusion, the cases will be classified as “None”

- For each case, timepoint, and imaging modality, the full case assessment included whether or not the images for that particular modality will be gradable as well as pathology assessments. These grading variables will be entered in the study specific database, per modality and visit. For each case and timepoint per imaging modality and visit, only one gradable variable assessment will be completed. Note that reference will be made here to timepoints because for some cases images could be provided for more than one timepoint (e.g., immediately after, a few weeks after the event). Each timepoint will be processed separately.

Figure 7-1 Imaging data flow: acquired images vs. reading center assessment



FA, Fluorescein Angiography; OCT, Optical Coherence Tomography.

This study is purely descriptive.

7.2 Setting

All cases of IOI, RV and/or RO reported to Novartis [redacted] involving brolucizumab use as per routine clinical practice for which images will be provided to Novartis will be considered for this study. Images will be collected globally until the cut-off date of 31 January 2021 from all countries where brolucizumab is approved.

7.3 Variables

Information on IOI and RV and/or RV will be collected using targeted FU checklists (Appendix 2). In addition to the information collection using the standard AE form, the following variables will be intended to be collected:

- Eye affected
- Number of days between last injection and event
- Number of injections prior to event
- Other medications prior to event
- Anti-VGF use prior to event
- Visual acuity before, at, and after event
- Medical history
- Treatment

Imaging related information on IOI and RV and/or RV will be provided by the reading center for each imaging modality using the imaging variable form and the case assessment form as presented in Appendix 2.

Primary Outcome

The main outcome will be the overall classification by the central reader based on the imaging data as RV only vs. RO only vs. RV+RO only vs. IOI vs. Not assessable vs. None. Table 7-1 provides the operational definition used for these classifications.

Table 7-1 Pathology by image modality – case classification and operational definition

Case classification based on imaging data and operational definition
Features Required for IOI (Case classification based on imaging: There is no RV or RO)

• OCT = vitreous hyper-reflective dots • FP = media opacities
Features Required for RV • FP = perivascular sheathing, kyrieleis plaque • FA = vascular leakage • ICG = early choroidal vessel hypercyanescence
Features Required for RO • FP = retinal vessel box-carring • FA = retinal arterial occlusion, retinal vein occlusion, retinal vessel box-carring, retinal ischemia, retinal neovascularization • ICG = choroidal hypocyanescent areas • OCT = inner retinal layer hyperreflectivity, paracentral acute middle maculopathy • OCT-A = superficial or deep capillary plexus ischemia

FA, fluorescein angiography; FP, fundus photography; ICG, indocyanine green; IOI, intraocular inflammation; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RO, Retinal vascular occlusion; RV, Retinal vasculitis.

Further Outcomes of interest

The following tables (Table 7-2, Table 7-3, and Table 7-4) list further key outcomes based on the imaging variable grading forms used in the evaluation of second component of the primary objective (i.e., anatomical location, type of occlusion and anatomical location in relation to the macula).

Table 7-2 Anatomical location by image modality

Anatomical location	Image modality	Definition/ item on check list
Retina (level 1)		Any terms under General retina, Vascular, Arterial, Vein, Ischemia, Vascular leakage (as defined below)
Vascular (level 2)		Arterial, Vein, Ischemia, Vascular leakage (as defined below))
Arterial (level 3)	FA	Retinal arterial occlusion – central, branch, peripheral; Retinal vessel boxcarring
	FP	Perivascular Sheathing =Yes and Vessel type=”Artery” or “Both”; Kyrieleis Plaques
	FA or FP	Retinal Vessel Boxcarring
Vein (level 3)	FA	Retinal vein occlusion - central, branch, peripheral
	FP	Perivascular Sheathing =Yes and Vessel type=“Vein” or “Both”
Ischemia (level 3)	FA	Retinal ischemia; Retinal Neovascularization
	OCT-A	Superficial Capillary Plexus Ischemia; Deep Capillary Plexus Ischemia
	OCT	Inner Retinal Layer Hyperreflectivity; Paracentral Acute Middle Maculopathy
		Inner Retinal Thinning
	OCT-A	Foveal Avascular Zone Perimeter Irregularity
Vascular leakage (level 3)	FA	Vascular leakage
General retina (level 2)	FP	Retinal Whitening; Retinal Hemorrhages; Cotton-wool Spots
	OCT	Cystoid Macular Edema
Vitreous (level 1)	FP	Media Opacities; Vitreous Hemorrhage
	OCT	Vitreous Hyper-reflective Dots
Choroid (level 1)	FA	Choroidal Hypoperfusion (Early Phase)

Anatomical location	Image modality	Definition/ item on check list
	ICGA	Early Choroidal Vessel Hypercyanescence; Choroidal Hypocyanescent Areas
	OCT-A	Choriocapillaris Ischemia
Optic nerve (level 1)	FA	Optic Nerve Head Hyperfluorescence
	FP	Optic Nerve Swelling
	ICGA	Optic Nerve Head Hypercyanescence
	OCT	Retinal Nerve fiber layer edema around optic nerve

FA, fluorescein angiography; FP, fundus photography; ICGA, indocyanine green angiography; OCT = optical coherence tomography; OCT-A = optical coherence tomography angiography.

Table 7-3 Type of occlusion by image modality

Type of occlusion	Image modality	Type of occlusion - Definition/ item on check list
Central	FA	Retinal Arterial Occlusion
	FA	Retinal Vein Occlusion
Branch	FA	Retinal Arterial Occlusion
	FA	Retinal Vein Occlusion
Periphery	FA	Retinal Arterial Occlusion
	FA	Retinal Vein Occlusion

FA, fluorescein angiography.

Table 7-4 Anatomical location in relation to the macula by image modality

Anatomical location in relation to the macula	Image modality	Location detail - Definition/ item on check list
Macula	FA or FP	Retinal Vessel Boxcarring
	FA	Vascular Leakage
	FA	Retinal Ischemia
	FA	Retinal Neovascularization
	FP	Perivascular Sheathing
	FP	Retinal Whitening
	FP	Cotton-wool Spots
	FP	Kyrieleis Plaques
	FP	Retinal Hemorrhages
	ICGA	Choroidal Hypocyanescent Areas:
	OCT or OCT-A	Include all features
		+all classified as Branch and Central
Mid-periphery	FA or FP	Retinal Vessel Boxcarring
	FA	Vascular Leakage
	FA	Retinal Ischemia:
	FA	Retinal Neovascularization
	FP	Perivascular Sheathing

	FP	Retinal Whitening
	FP	Cotton-wool Spots
	FP	Kyrieleis Plaques
	FP	Retinal Hemorrhages
	ICGA	Choroidal Hypocyanescent Areas:
Periphery	FA	Retinal Arterial Occlusion
	FA	Retinal Vein Occlusion
	FA or FP	Retinal Vessel Boxcarring
	FA	Vascular Leakage
	FA	Retinal Ischemia:
	FA	Retinal Neovascularization
	FP	Perivascular Sheathing
	FP	Retinal Whitening
	FP	Cotton-wool Spots
	FP	Kyrieleis Plaques
	FP	Retinal Hemorrhages
	ICGA	Choroidal Hypocyanescent Areas:

FA, fluorescein angiography; FP, fundus photography; ICGA, indocyanine green angiography; OCT = optical coherence tomography; OCT-A = optical coherence tomography angiography.

7.4 Data sources

The data for this study will be retrieved from two data sources: imaging variables from Reading center assessment forms and the patients demographics and clinical features from the Novartis Patient Safety database ([redacted]) provided by Novartis AG.

The imaging database will be set up for this study and contains the grading variable for the images provided to the reading center.

The Novartis Patient Safety database will be used to retrieve the case classification by reading center as RV only vs. RO only vs. RV+RO only vs. IOI vs. Not assessable vs. *None* and further case information (e.g., patient characteristic, visual acuity).

Data will be linked using the Novartis Patient Safety database ([redacted]) case ID.

[redacted] will perform the analysis according to the contract agreement in the Novartis programming environment (GPSII).

7.5 Study size/power calculation

This analysis will be descriptive in nature and all cases in the respective cohort will be included.

Based on the current data, the number of events of interest remained limited in the Novartis Patient Safety database, any presented % will be therefore associated with wide variability. Table 7-5 provides the precision-based statistics by sample size based on binomial exact method.

Table 7-5 Precision-based Statistics by Sample Size

Cases in Cohort (n)	Case with Characteristics (n)	Precision	
		% Point Estimate (95% CI)	CI Width
20	1	5.0 (0.1, 24.9)	24.7
	5	25.0 (8.7, 49.1)	40.4

Cases in Cohort (n)	Case with Characteristics (n)	Precision	
		% Point Estimate (95% CI)	CI Width
50	1	2.0 (0.1, 10.6)	10.6
	5	10.0 (3.3, 21.8)	18.5
	25	50.0 (35.5, 64.5)	28.9
100	1	1.0 (0.0, 5.4)	5.4
	5	5.0 (1.6, 11.3)	9.6
	25	25.0 (16.9, 34.7)	17.8

CI, confidence interval.

7.6 Data management

Data collected through the targeted checklists will be entered into the Novartis Patient Safety database per Novartis SOPs governing PV safety procedures.

Imaging grading variables will be processed centrally by the reading center ([redacted]) and the results will be sent electronically to Novartis.

7.7 Data analysis

All analyses will be performed by [redacted]. Data will be analyzed and performed by Novartis using SAS version 9.3 or higher on the GPSII Release 5.3 Production environment.

A statistical analysis plan (SAP) detailing the analysis to be conducted will be developed.

As described herein, only cases with the event of interest and available images will be sent for independent assessment. Consequently, no incidence rate for events of interest will be derived.

Distributions of continuous variables will be summarized with means ± standard deviations (SD), medians, interquartile range and absolute range. Categorical variables will be summarized with proportions.

7.7.1 Case disposition/attrition

The image quality and quality issues as reported by the reading center (e.g., poor focus; Poor field placement; Eyelid or eyelash artifact; Poor color balance; Overexposed; Underexposed; Undersaturated; Oversaturated; Other) will be summarized by image modality.

The number of gradable cases will be summarized by image modality.

7.7.2 Primary objective

For the gradable cases, the case classification based on imaging data (“IOI” vs. “RV only” vs. “RO only” vs. “RV+RO only” vs. “None” vs. “RV and/or RO” vs. “None”) will be summarized overall and by image modality.

Anatomical location and sub-location (Retina (further classified as general vs. vascular) vs. Vitreous vs. Choroid vs. Optic nerve) were summarized by imaging modality and case classification based on imaging data.

Type of occlusion (Central vs. Branch vs. Periphery) will be summarized by case classification based on imaging data.

Anatomical location in relation to macula (Macula vs. Mid-periphery vs. Periphery) and location details will be summarized by case classification based on imaging data.

The extent of involvement as collected via imaging grading variable will be summarized by Anatomical location and reading center case classification.

7.7.3 Exploratory objective

Based on data availability, the following data obtained from the Novartis Patient Safety database will be summarized by case classification based on imaging data:

- Patient characteristics (age, gender, ethnicity, country), treatment of AEs (action taken), events information (seriousness, seriousness criteria, outcome, and worse outcome).
- Further case characterization (affected eye, time since last brolucizumab injection, time since first brolucizumab injection, number of brolucizumab injections, prior anti-VGF use and treatment)
- Visual outcome (i.e., classified as with vision loss vs. with vision impairment vs. without reported vision loss/impairment.)

Imaging features by visual outcome may be analyzed, if appropriate (i.e., if observations made in the primary objective are clinically relevant).

7.7.4 Adjustment for multiplicity and testing strategies

Not applicable. This study is purely descriptive and no hypothesis will be tested.

7.7.5 Subgroups of interest and specific analyses conducted in these subgroups

The following subgroups will be considered:

- Cases reported [redacted]

No missing data imputation will be performed.

7.8 Quality control

The SOPs for PV will be followed to perform quality control of the data entered into the Novartis patient safety database.

Data recording and documentation retention will be followed as standard operating procedures defined for collection and retention of data in the Novartis Patient Safety database.

7.9 Limitations of the research methods

As this review of images will be performed on spontaneously reported AEs of interest arising from routine clinical practice, some limitations, inherent to the methodology, are listed below:

- Limitations inherent to post-marketing reporting systems include under-reporting, incompletely documented cases and cases without adequate imaging information.
- Reporting practices vary by country, physician, the type of event and the visual outcomes.
- This study did not allow determination of incidences or incidence rates.
- Ocular images may not be captured at the time of event. In addition, reference images i.e. obtained before the events or images capturing event outcome may not be available.
- No standardization of images; peripheral images may not be available for all cases.
- Anterior chamber (A/C) cells and flare cannot be assessed via imaging in majority of cases as these are commonly noted on clinical examination and not via imaging due to the limited availability of relevant imaging.
- Clinical information and visual acuity information may be incomplete or unavailable.
- Some of the observed imaging parameters may not necessarily associated with clinical symptoms and may lack clinical significance.
- Many of the parameters that will be used for this study are not fully validated and may not be assessed by physicians in the context of routine clinical practice.

Despite the limitations, the generated data will provide Novartis insights on the imaging parameters of the inflammatory events occurring in the post-marketing setting and help Novartis better understand and characterize this risk.

7.10 Other aspects

Not applicable

8 Protection of human subjects

Confidentiality of information will be ensured by anonymization of the data. No identifiable information will be provided to Novartis, directly or indirectly via third parties of any nature.

Primary collection of data will be through spontaneous AE reporting.

1. Consent for review by reading center will be considered implicit as the purpose of collection is the evaluation of the individual case reported by the health care practitioner (purpose also will be detailed in the instructions and request for images).

In addition, in the targeted follow-up checklist consent for further use of the images will be requested as described below:

Utilization of anonymized images for:

1. Review and publishing by independent external experts
2. Use by Novartis for medical education purposes, in publications and/or presentations
3. De-identification of images to remove all personal health identifiers will be performed by dedicated Novartis personnel immediately upon receipt and prior to transfer to the reading center.

This study will be based on secondary use of data, therefore informed consent will not be required.

Regulatory and ethical compliance

This study will be designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016),[15] the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2007),[16] and with the ethical principles laid down in the Declaration of Helsinki.[17]

This study fulfilled the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and followed the 'ENCePP Code of Conduct' (European Medicines Agency 2016).[18]

9 Management and reporting of adverse events/adverse reactions

As this is an analysis based on secondary use of data, reporting will be provided on an aggregate level only; no reporting on an individual case level is required. The individual cases are already included in Novartis Safety Database and will already be reported to Health Authorities. Relevant findings from the study report will be included in the periodic aggregated regulatory reports (PSURs) submitted to Health Authorities.

[redacted]

11 References

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