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Non-Interventional Study Final Report

# 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

## REDACTED STUDY REPORT


| | |
|---|---|
| Author | [redacted], MD<br>Novartis Pharmaceuticals Corporation |
| Document Status | Final |
| Date of final version of the study report | 22-Feb-2022 |
| EU PAS register number | EUPAS41014 |

**PASS information**

| | |
|---|---|
| **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 |
| **Version identifier of the final study report** | v00 |
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| **EU PAS register number** | EUPAS41014 |
| **NIS Type** | NIS with secondary use of data |
| **Active substance** | Brolucizumab |
| **Medicinal product** | Beovu®, Pagenax®, Vsiqq® Solution for Injection (brolucizumab) |
| **Product reference** | Unique Product Identifier: 000206<br>MA numbers: EU/1/19/1417/001-002 |
| **Procedure number** | Not applicable |
| **Marketing authorization holder** | Novartis Pharma AG |
| **Joint PASS** | No |
| **Research question and objectives** | This study provides real-world overview of the imaging features from images collected at time 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. |
| **Countries of study** | Global PV program (including Australia, Canada, Germany, Japan, Malaysia, Portugal, Switzerland, United Arab, United States) |
| **Main author** | [redacted], MD<br>Novartis Pharmaceuticals Corporation |

## Marketing authorization holder

| | |
|---|---|
| Marketing authorization holder | Novartis Pharma AG<br>Lichtstrasse 35<br>4056 Basel<br>Switzerland |
| MAH contact person | [redacted], [redacted],<br>[redacted]<br>[redacted]<br>[redacted]<br>[redacted] |

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# 1 Abstract

**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

**Version and date**

v00, 22-Feb-2022

**NIS Type**

NIS with secondary use of data

**Name and affiliation of main author**

[redacted], MD

Novartis Pharmaceuticals Corporation

**Keywords**

Brolucizumab, Neovascular age-related macular degeneration, occlusive retinal vasculitis, retinal vasculitis (RV) and/or retinal vascular occlusion (RO), ocular images

**Rationale and background**

Brolucizumab has been approved in the US in Oct-2019, Europe in Mar-2020, Japan in May-2020, and in other countries for the treatment of nAMD. Events of occlusive retinal vasculitis following the use of brolucizumab in the post-marketing setting were first reported from the US 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" was confirmed in Apr-2020.

Novartis has developed an enhanced Pharmacovigilance (PV) program to enable better characterization of these aforementioned AEs reported in the post-marketing setting with brolucizumab use. The enhanced PV program included the collection of ocular images and review by an external reading center.

For this study, a summary report of findings was provided for each eye case from the external reading center to Novartis, including an overall imaging-based eye case classification. The assessment of location and extent of the event, as well as the pathological features on the images were also provided per eye case.

**Research question and objectives**

The purpose of this retrospective study was to describe the imaging findings based on a standardized reading center review of eyes so as to better characterize the risk of inflammatory events arising from use of brolucizumab in routine clinical practice through the analysis of independently reviewed ocular imaging data obtained from cases with reports of IOI, RV and/or RO.

The aim of the study was to get a better understanding of the most commonly observed imaging features obtained from images collected at the time of the AEs of interest and reported to Novartis Patient Safety.

**Study design**

This non-interventional descriptive study was undertaken to better understand the most common imaging features associated with inflammation arising in the post-marketing setting when brolucizumab was prescribed in routine clinical practice.

Whenever an AE report pertaining to RV and/or RO was reported to Novartis Patient Safety, a follow-up check list (targeted follow-up checklists [TFUs]) was sent by Novartis to the reporter. The reporter was encouraged to share all available images obtained as part of clinical practice, irrespective of the timing or event (i.e. images before, during, and after event could be provided). The focus and main efforts of this data collection was on adverse events of RV and/or RO; for other IOI only events, the

images were not actively requested in the case documentation process, however in some cases these were spontaneously reported by the reporter.

All images obtained from Feb-2020 up to 31-Jan-2021 were reviewed in a standardized manner by an external reading center. Dedicated grading lists were developed for each of the image modalities: Fluorescein Angiography (FA), Fundus Photography (FP), Indocyanine Green Angiography (ICGA), Optical Coherence Tomography (OCT), and OCT Angiography (OCT-A).

For each eye case, the reading center provided the following information:

1. An overall independent eye case classification based on all provided imaging data ("**RV only"** vs. "**RO only"** vs. "**RV + RO only"** vs**. "IOI** only (involving the posterior segment)" vs. "**Not assessable"** vs. "**None"**) acquired at the time the event was provided. Case was deemed to be "Not assessable" when image quality concerns prevented grading and "None" when there were no imaging features of IOI, RV or RO.
2. For each eye case, time point and imaging modality, the eye case assessment included whether the image for that particular modality was gradable as well as the pathological features on the respective image, based on their respective grading lists. For each eye case, per imaging modality and timepoints (i.e. visit), one gradable variable assessment was completed. Note that reference was made here to timepoints because images could be provided for more than one timepoint (e.g. immediately after, a few weeks after the event). Each timepoint was processed separately. Only images from the treated and affected eye taken at the time of event were included in the results presented in this report body.

**Setting**

Post-marketing eye cases of RV and/or RO reported to Novartis Patient Safety from which ocular images were requested and provided to Novartis until 31-Jan-2021, from all countries where brolucizumab was approved and used per routine clinical practice, were considered for this study. Of note, the few IOI cases, for which images were provided, were also included in the analysis.

These eye case images provided to Novartis were reviewed by an external reading center [redacted]-referred to as 'reading center' hereafter).

**Subjects and study size, including dropouts**

The analysis was descriptive and all cases from the retrospective cohort were included. As this study used secondary data from Novartis Patient Safety database, there was no specified set of subject population in this study and all cases with event of interest with available images were retrieved.

There was no specific targeted sample size.

**Variables and data sources**

The variable sare discussed below:

a. **Imaging Variables:** The reading center assessed the presence and extent / location of the findings as displayed in Table 1-1:

**Table 1-1 Imaging variables by imaging modality**

| FP | FA | OCT | OCTA | ICGA |
|---|---|---|---|---|
| Perivascular sheathing | Retinal arterial occlusion | Vitreous/ preretinal hyperreflective dots | Foveal avascular zone perimeter irregularity | Early choroidal vessel hypercyanescence |
| Retinal vessel boxcarring | Retinal vein occlusion | Inner retinal layer hyperreflectivity | Superficial capillary plexus ischemia | Choroidal hypocyanescent areas |

| FP | FA | OCT | OCTA | ICGA |
|---|---|---|---|---|
| Retinal whitening | Vascular leakage | Paracentral acute middle maculopathy | Deep capillary plexus ischemia | Optic nerve head hypercyanescence |
| Cotton wool spots | Retinal ischemia | Cystoid macular edema | Choriocapillaris ischemia | |
| Kyrieleis plaques | Optic nerve head hyperfluorescence | Retinal nerve fiber layer edema around optic nerve | | |
| Retinal hemorrhage | Retinal vessel boxcarring | Inner retinal thinning | | |
| Optic nerve swelling | Retinal neovascularization | | | |
| Media opacities | Choroidal hypoperfusion (Early phase) | | | |
| Vitreous hemorrhage | | | | |

b. **Case Classification:** The overall eye case classification by the reading center based on the imaging data was RV only vs. RO only vs. RV + RO only vs. IOI vs. Not assessable vs. None. Table 1-2 provides the operational definition used for these classifications.

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

| Case classification based on imaging data and operational definition |
|---|
| **Features (at least one) required for IOI (in addition to no features of RO or RV)**<br>• OCT = vitreous hyper-reflective dots<br>• FP = media opacities |
| **Features required for RV (at least one)**<br>• FP = perivascular sheathing, Kyrieleis plaque<br>• FA = vascular leakage<br>• ICG = early choroidal vessel hypercyanescence |
| **Features required for RO (at least one)**<br>• FP = retinal vessel box-carring<br>• FA = retinal arterial occlusion, retinal vein occlusion, retinal vessel box-carring, retinal ischemia, retinal neovascularization<br>• ICG = choroidal hypocyanescent areas<br>• OCT = inner retinal layer hyperreflectivity, paracentral acute middle maculopathy<br>• OCT-A = superficial or deep capillary plexus ischemia |
| **Not assessable**<br>• image quality concerns prevented grading |
| **None**<br>• no imaging features of IOI, nor RV nor RO |

**Data sources**

The data for this study was retrieved from two data sources: Imaging data and the Novartis Patient Safety database (ARGUS) provided by Novartis.

The imaging database set up for this study contained the grading variables for the images that were provided to the reading center.

Further eye case information retrieved from ARGUS was limited to gender, age and country only.

**Statistical methods**

Since only cases with events of interest and with available images were sent for independent assessment, no incidence rates could be derived. Categorical variables were summarized with proportions.

Anatomical location and sub-location, type of occlusion in the eye were summarized by eye case classification based on imaging data and imaging modality. The extent of involvement was also analyzed.

Analyses were performed at eye case level i.e. treating each eye in the same case independently.

**Results**

- A total of 475 gradable images were received from 222 eye cases in 198 patients. The most common images provided were fundus photographs followed by OCTs and then fluorescein angiograms. This was the largest descriptive analysis of imaging features associated with brolucizumab -related inflammation, taken at the time of event occurrence
- The majority of cases were classified as RV only (n=72 cases), followed by RV+RO only (n=63 cases), and then posterior segment IOI (n=31 cases). Additional n=9 cases were classified as RO only and n=47 cases as None.
- The most common imaging variable seen in cases with RV and/or RO patients with an abnormality seen on: FA was vascular leakage (90% cases); on FP was perivascular sheathing (83% cases), and on OCT was hyperreflective dots in the vitreous (64%).
- Majority of the cases had macular involvement. Around 13.9% of eyes had findings sparing the macula.
- Retinal occlusion was mainly arterial; more branch retinal artery occlusion than central retinal artery occlusion; peripheral vessels were involved in about 1/4th of eye cases and multiple vessels more likely than single vessel.

**Discussion**

The analysis describes the most common imaging features associated with inflammation in patients treated with brolucizumab in the post-marketing setting. A total of 475 gradable images were received from 222 eye cases in 198 patients. The most common images provided were FP (n=172) followed by OCT (n=166) and then FA (n=105). The most common imaging variable seen in cases with RV and/or RO with an abnormality on FA was vascular leakage (90% cases); on FP was perivascular sheathing (83% cases), and on OCT was hyperreflective dots in the vitreous (64%).These are well-known features of inflammation. However, there were a few patients with less-common findings such as Kyrielies plaques etc. Additionally, while majority of the cases had macular involvement, at least 13.9% of eyes had findings sparing the macula. Given the post-marketing nature of this observational study, limitations need to be considered when interpreting the results. In particular, the voluntary reporting may lead to potential selective reporting and results may not be representative for all cases. In addition, no comparator images, from eyes without RV and/or RO, were available. Nonetheless, the key strengths of this study are the standardized interpretation of these retinal images and the standardized classification based on imaging along with being the largest descriptive analysis of imaging features associated with inflammation occurring in patients treated with brolucizumab in routine clinical practice and taken at the time of event occurrence, and therefore providing insights into the spectrum of inflammatory changes and anatomical features.

**Conclusion**

This study expanded the knowledge of the real world practice related to handling of the inflammatory events with respect to ophthalmological images obtained at the time of the inflammatory event in patients treated with brolucizumab. This is the largest descriptive analysis of imaging features in these cases and were analyzed in a standardized manner. Accordingly, this dataset provides valuable information by increasing our understanding of the spectrum of posterior segment inflammatory changes occurring in patients treated with brolucizumab and may further guide clinical practice by informing physicians on both common and uncommon features indicative of an inflammatory event in order to detect and further treat the events.

**Marketing Authorization Holder**

Novartis AG, Lichtstrasse 35,

4056 Basel, Switzerland

**Name(s) and Affiliation(s) of Principal Investigator(s)**

# 2 List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AMD | Age-related macular degeneration |
| CI | Confidence Interval |
| EU | European Union |
| FA | Fluorescein angiography |
| FDA | Food & Drug Administration |
| FP | Fundus photography |
| HA | Health Authority |
| ICG | Indocyanine green |
| IEC | Independent Ethics Committee |
| IOI | Intraocular Inflammation |
| IRB | Institutional Review Board |
| MAH | Marketing Authorization Holder |
| nAMD | Neovascular Age-related macular degeneration |
| NIS | Non-Interventional Study |
| NVS | Novartis |
| OCT | Optical coherence tomography |
| OCT-A | Optical coherence tomography angiography |
| PASS | Post-Authorization Safety Study |
| PDT | Photodynamic therapy |
| PV | Pharmacovigilance |
| RO | Retinal vascular occlusion |
| RV | Retinal vasculitis |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SD-OCT | Spectral Domain Optical Coherence Tomography |
| SOP | Standard Operating Procedure |
| VEGF | Vascular endothelial growth factor |

# 3 Investigators

[redacted]

For details refer to Appendix 1.

# 4 Other responsible parties

The signatures of the principal Investigator, are provided in Appendix 1-Investigator signatory page. The responsible parties are listed in Table 4-1.

**Table 4-1 Responsible parties**

| | |
|---|---|
| **Study lead** | [redacted] MD |
| **Main protocol authors** | [redacted] |
| **Main report authors** | [redacted] ; |
| **MAH contact person** | [redacted] |
| **Statistical data analysis** | [redacted] |

# 5 Milestones

The planned and actual dates of study milestones are presented in Table 5-1.

**Table 5-1 Study milestones**

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Start of data collection | 17-May-2021 | 24-Aug-2021 | Data available from the reading center |
| End of data collection (Last date of data collection) | 15-Jun-2021 | 04-Jan-2022 | Date of last data transfer |
| Registration in the EU PAS register | 10-May-2021 | 12-May-2021 | None |
| Final report of study results | 15-Sep-2021 | 17-Feb-2022 | None |

# 6 Rationale and background

Brolucizumab has been approved in the US in Oct-2019, Europe in Mar-2020, Japan in May-2020, and in other countries for the treatment of neovascular (wet) nAMD (EU Beovu SmPC 2020, USPI Beovu 2019, Swiss Beovu PI 2021, Australian Beovu PI 2020, Canada Beovu product monograph 2021, PMDA Japan 2019). Events of occlusive retinal vasculitis

following the use of brolucizumab in the post-marketing setting were first reported from the US 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" was confirmed in Apr-2020 (Mones et al 2020, Baumal et al 2020a, Baumal et al 2020b).

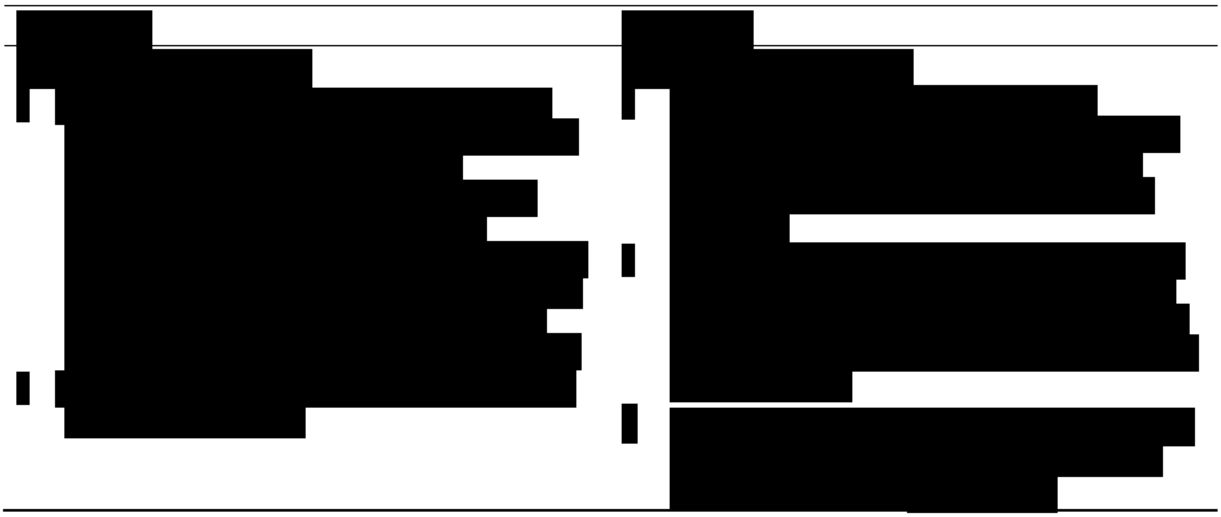
Novartis developed an enhanced PV program to enable better characterization of these aforementioned AEs reported in the post-marketing setting with brolucizumab use (The enhanced PV program included the collection of ocular images and review by an external reading center. Dedicated grading lists were developed for each of the following image modalities: FA, FP, ICGA, OCT, and OCT-A. In this study, a summary report of findings was provided for each case, including an overall imaging-based eye case classification. The assessment of location and extent of the event, as well as the pathological features on the images were summarized per eye case.

# 7 Research question and objectives

The aim of the study was to get a better understanding of the most commonly observed imaging features obtained from images collected at the time of the AEs of interest, reported to Novartis Patient Safety and reviewed in a standardized manner by the reading centre, so as to better characterize the risk of inflammatory events arising from use of brolucizumab in routine clinical practice. The objectives and endpoints are listed in Table 7-1.

**Table 7-1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary Objective:**<br>To characterize brolucizumab AEs of interest in terms of independent case classification based on imaging data<br>A. Distribution (breakthrough) of imaging classification of the cases<br>B. Distribution (breakthrough) of location and findings by imaging modality | **Primary Endpoint:**<br>1. Eye case classification based on imaging data (i.e. "IOI" vs. "RV only" vs. "RO only" vs. "RV+RO only" vs. None).<br>2. For each imaging finding, finding present by event type (RV/RO) as per independent review:<br>• Anatomical location and sub-location-Retina (further classified as general vs. vascular), Vitreous, Choroid, and Optic nerve;<br>• Type of occlusion (Central, Branch, and Periphery);<br>• Anatomical location in relation to macula (Macula, Mid-periphery, and Periphery) and location<br>• Extent of involvement |



* The ability to analyze exploratory endpoints was entirely based on the availability to retrieve the information from the Novartis Patient Safety database in a systematic manner allowing programmatical exploitation. Since for PV purposes, data are captured on a case level rather than eye case level and a case possibly involving several events not necessarily assessed in a same way by the reporter as per central review, and due to the lack of standardized data collection and entry, **the patient characteristics have been limited to age, gender and country and no further characteristics could be provided**. This constitutes a change to the planned analysis and is discussed in Section 9.8.

# 8 Amendments and updates to the protocol

The protocol was amended once to include formatting changes, specify that the classification was performed at eye rather than at patient level and introduce the Japan subgroup analysis (refer Appendix 2).

Upon data inspection, a further change was introduced in the data capture: some cases were reported for the patients treated with brolucizumab bilaterally, in other patients, events occurred bilaterally. The focus of this study was images available for treated and affected eyes shared with the reading center. As a consequence, unlike planned in the protocol, the overall independent eye case classification was directly retrieved from the imaging database i.e. allowing the distinction between left and right eye rather than from Novartis Patient Safety database.

# 9 Research methods

## 9.1 Study design

This non-interventional descriptive study was carried out to better understand the most commonly observed imaging features obtained from images collected at the time of the AEs of interest, reported to Novartis Patient Safety. They were reviewed in a standardized manner by the reading center, so as to understand the nature of the RV and/or RO with or without inflammation and with or without vision loss reported with the use of brolucizumab.

Whenever an AE report pertaining to RV and/or RO was reported to Novartis Patient Safety, a follow up check list (targeted follow-up checklists [TFUs]) was sent by Novartis to the reporter.

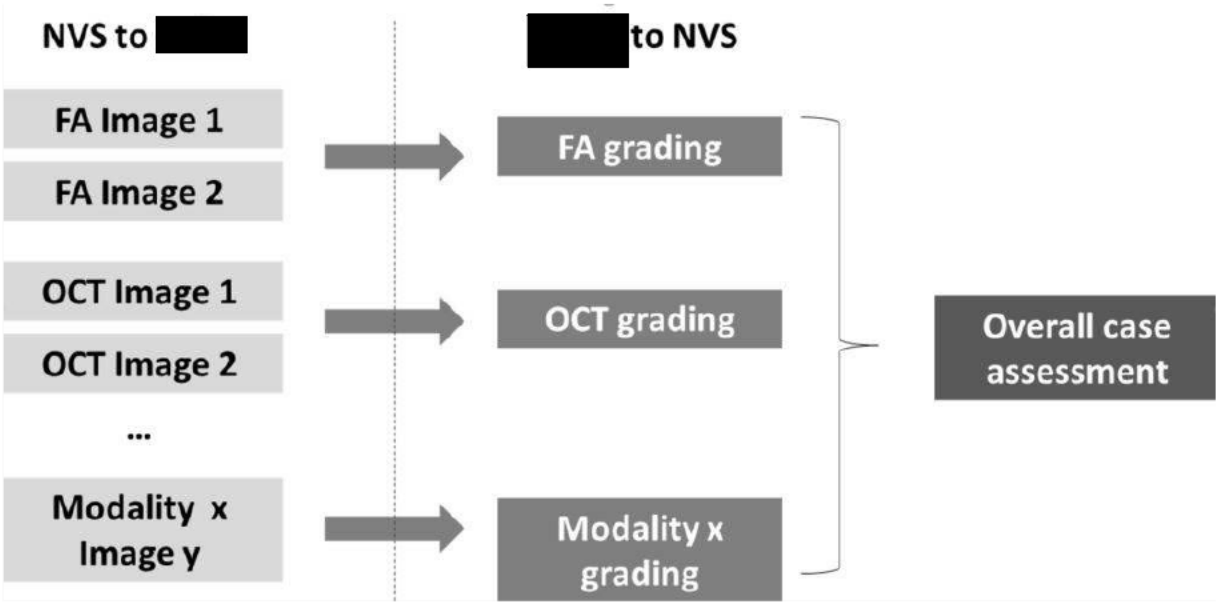
The reporter was encouraged to share all available images obtained as part of clinical practice, irrespective of the timing or event (i.e. images before, during, and after event could be provided). The focus and main efforts of this data collection was on adverse events of RV and/or RO; for other IOI only events, the images were not actively requested in the case documentation process, however in some cases these were spontaneously reported by the reporter.

All images obtained for the RV + RO cases from Feb-2020 up to 31-Jan-2021 were reviewed in a standardized manner by an external reading center. Dedicated grading lists were developed for each of the image modalities: FA, FP, ICGA, OCT, and OCT-A. No restriction was made in term of type of images collected or method of capture (i.e. any image acquired on any platform could be shared such as FP and FA, OCT, OCT-A, and ICGA).

For each affected and treated eye case, the reading center provided the following information (as illustrated in Figure 9-1):

- An overall classification of the eye based on all provided imaging data acquired at the time of event as RV only vs. RO only vs. RV and RO only vs. IOI only vs. Not assessable vs. None.
- For each eye case, time point and imaging modality, the full eye case assessment included whether or not the images for that particular modality were gradable, as well as the pathological features on the respective image. These grading variables were entered in the database per imaging modality and visit (timepoint). For each eye case, per imaging modality and timepoints (i.e. visit), only one gradable variable assessment was completed Note that reference was 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 was processed separately. Only images from the treated and affected eye taken at the time of event were included in the results presented in this report body.

**Figure 9-1 Imaging data flow: acquired images vs. reading center assessment**



## 9.2 Setting

Post-marketing eye cases of RV and/or RO reported to Novartis Patient Safety from which ocular images were requested and provided to Novartis until 31-Jan-2021, from all countries where brolucizumab was approved and used per routine clinical practice, were considered for this study. Of note, the few IOI cases for which images were provided, were also included in the analysis. Images obtained were as taken by the physician according to their clinical practice.

These eye case images were provided to Novartis and reviewed by an external reading center – [redacted] (mentioned as 'reading center' throughout this CSR).

## 9.3 Subjects

As this study used secondary data from Novartis Patient Safety database, there was no specified set of subject population in this study and all cases with event of interest and available images were retrieved.

## 9.4 Variables

Imaging related information on IOI and RV and/or RO was provided by the reading center for each imaging modality using the imaging variable form and the case assessment form (as presented in Appendix 1-case assessment form).

The main outcomes were the overall eye case classification by the central reader and the presence, extent and location of findings based on the imaging data.

### 9.4.1 Overall eye case classification

Cases were classified as RV only vs. RO only vs. RV+RO vs. IOI vs. Not assessable vs. "None". Table 9-1 provides the operational definition used for these classifications.

**Table 9-1 Pathology by image modality – eye 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)<br>• OCT = vitreous hyper-reflective dots<br>• FP = media opacities<br>Features required for RV<br>• FP = perivascular sheathing, Kyrieleis plaque<br>• FA = vascular leakage<br>• ICG = early choroidal vessel hypercyanescence<br>Features required for RO<br>• FP = retinal vessel box-carring<br>• FA = retinal arterial occlusion, retinal vein occlusion, retinal vessel box-carring, retinal ischemia, retinal neovascularization<br>• ICG = choroidal hypocyanescent areas<br>• OCT = inner retinal layer hyperreflectivity, paracentral acute middle maculopathy<br>• OCT-A = superficial or deep capillary plexus ischemia |

| Case classification based on imaging data and operational definition |
|---|
| Not assessable<br>• image quality concerns prevented grading<br>None<br>• no imaging features of IOI, RV, or RO |

*the classification was limited to signs of posterior segment involvement

### 9.4.2 Presence, extent and location of findings

Table 9-2, Table 9-3 and Table 9-4 list the 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 9-2 Anatomical location by image modality**

| Anatomical location | Image modality | Definition/ item on check list |
|---|---|---|
| **Retina (level 1)** | | Any terms under Vascular, General retina (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 box-carring |
| | FP | Perivascular Sheathing =Yes and Vessel type=”Artery” or “Both”; Kyrieleis Plaques |
| | FA or FP | Retinal Vessel Box-carring |
| **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; Foveal Avascular Zone Perimeter Irregularity |
| | OCT | Inner Retinal Layer Hyperreflectivity; Paracentral Acute Middle Maculopathy; Inner Retinal Thinning |
| **Vascular leakage (level 3)** | FA | Vascular leakage |
| **General retina (level 2)** | FP | Retinal Whitening; Retinal Hemorrhages; Cotton-wool Spots |
| | OCT | Cystoid Macular Edema |

| Anatomical location | Image modality | Definition/ item on check list |
|---|---|---|
| **Vitreous (level 1)** | FP | Media Opacities; Vitreous Hemorrhage |
| | OCT | Vitreous Hyper-reflective Dots |
| **Choroid (level 1)** | FA | Choroidal Hypoperfusion (Early Phase) |
| | 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 |

**Table 9-3 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 |

**Table 9-4 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 Box-carring |
| | 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 OCTA | Include all features<br>+all classified as Branch and Central in Table 9-3 |
| **Mid-periphery** | FA or FP | Retinal Vessel Box-carring |
| | 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 Box-carring |
| | 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: |

## 9.5 Data sources and measurement

The data for this study was retrieved from two data sources: imaging data and the Novartis Patient Safety database (ARGUS) provided by Novartis.

The imaging database was set up for this study and contained the grading variables for the images from the treated and affected eyes that were provided to and read by the reading center. The overall eye case classification was also retrieved from this database (unlike planned in the protocol, see Section 8).

The Novartis Patient Safety database (ARGUS) was used to retrieve further case information which included age, gender and country. In ARGUS, following usual PV practice, information for both eyes were entered under the same case ID. Data between the imaging database and ARGUS was therefore linked using the ARGUS case number irrespective of the eye information.

## 9.6 Bias

This was a retrospective analysis of imaging and clinical features from patients treated with brolucizumab in a post-marketing setting.

Bias inherent to reporting in a **PV system** apply:

- Spontaneous report data are collected passively relying on healthcare professionals and patients to recognize suspected adverse outcomes.
- Voluntary reporting may lead to potential selective reporting and result may not be representative for all cases.
- The information is reported at patient case level rather than eye case level with details on eye level provided as part of narratives.
- The information is not necessary captured in a structured manner (e.g. visual acuity is not standardized; in real world, the timing of assessment cannot be imposed).
- Reporting practices vary by country, physician and type of event.
- Under-reporting of cases, incompletely documented cases, and cases without adequate imaging information is frequent.

In addition to the PV system bias, the other biases were:

i. The majority of adverse events reported to Novartis in the post-marketing setting was IOI. However, images were requested only from patients with RV/RO and thus the proportion of IOI cases may not be an accurate representation in this dataset. Even amongst this population, images were not provided in all cases.
ii. The image collection was not systematic and only a set of cases included images.
iii. No control images, i.e. no unaffected eyes were considered.
iv. All images provided by physician were accepted, therefore there was no standardization of images or image acquisition protocols.
v. Mid-peripheral and Peripheral wide field images were not available for all cases.
vi. All imaging modalities were not available for each case. Additionally, there may have been features seen on ocular examination that may not have been captured via imaging and are therefore not included in the analysis.
vii. Limited time period (only 1-2 months) for collecting images from intraocular inflammation patients.

## 9.7 Study size

This analysis was descriptive in nature and all cases in the respective cohort were included.

The number of events of interest remained limited in the Novartis Patient Safety database, any presented % are therefore associated with wide variability.

Table 9-5 provides the precision-based statistics by sample size based on binomial exact method.

**Table 9-5 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 |
| 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 |

## 9.8 Data transformation

Grouping of categories was applied as per Section 9.4.

## 9.9 Statistical methods

Data analysis was performed internally by Novartis (CTS CONEXTS group as listed in Table 4-1), using SAS version 9.4 on the Novartis Global Programming System (GPSII).

### 9.9.1 Main summary measures

Only cases with the event of interest and available images were sent for independent assessment. Consequently, no incidence rate for the event of interest (i.e. RV, RO, IOI) could be derived.

All analyses related to imaging were conducted at eye case level, i.e. treating eyes independently even if reported as part of the same ARGUS case.

Categorical variables will be summarized with proportions.

### 9.9.2 Main statistical methods

#### Analysis sets

The cases were divided into four analysis sets as detailed below.

The analysis set focused on images obtained just after the event marked as Visit 1 in the dataset. For cases with images provided at several timepoints, data obtained for the other timepoints were listed only.

**All images cohort**

- The "All images cohort" included all imaging modalities per eye case sent to the reading center.
- This set was mainly used to describe image quality.
- The unit of observation was modalities per eye case i.e. a given eye case could involve several imaging modalities. The modality is referred to as "images" in the below since the information was provided at that level.

**Gradable images cohort**

- The primary analysis cohort was the gradable images cohort i.e. images for which the quality was sufficient for the reading center to determine grading.
- The unit of observation was modalities per eye case i.e. a given eye case could involve several imaging modalities. The modality is referred to as "images" in the below since the information was provided at that level.

**All images eye case cohort**

- The "All images eye case cohort" included all eye cases for which an overall independent case classification was determined, including the "Not assessable" ones.
- The unit of observation was eye cases.

**Gradable images eye case cohort in short "Gradable case cohort"**

- The "Gradable case cohort" included all eye cases for which an overall independent eye case classification was determined, excluding the "Not assessable" ones.
- Note that in this cohort, an eye case could be marked as "assessable" even if some image modalities were non-gradable.
- The unit of observation was eye cases.

### Case disposition/attrition

Starting with the "All images cohort", the number of images entering the "Gradable images cohort" were summarized by image modality.

### Primary objective

For the gradable cases, the eye case classification based on imaging data ("IOI" vs. "RV only" vs. "RO only" vs. "RV+RO only" vs. "RV and/or RO" vs. "None") was summarized overall and by image modality. The further category "RV and/or RO" included the cases classified as "RV only" or "RO only" or "RV+RO only" by the reading center.

Using groupings as defined in Section 9.4,

- 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 eye case classification based on imaging data.
- Type of occlusion (Central vs. Branch vs. Periphery) was summarized by eye case classification based on imaging data.

- Anatomical location in relation to macula (Macula vs. Mid-periphery vs. Periphery) and location details were summarized by eye case classification based on imaging data.
- The extent of involvement as collected via imaging grading variable was summarized by anatomical location and reading center eye case classification.
- Grading variables were summarized by modality and reading center eye case classification.

### Exploratory objective

The ability to analyze the exploratory endpoints was entirely based on the availability to retrieve the information from the Novartis Patient Safety database in a systematic manner allowing programmatical exploitation. Since for PV purposes, data are captured on a case level rather than eye case level and a case possibly involving several events not necessarily assessed in a same way by the reporter as per central review, and due to the lack of standardized data entry, the patient characteristics have been limited to age, gender and country and no further characteristics were provided.

### Subgroups of interest and specific analyses conducted in these subgroups

The following subgroup was considered:

- Cases reported from Japan

## 9.9.3 Missing values

No missing data imputation was performed in this study.

## 9.9.4 Sensitivity analyses

Not applicable.

## 9.9.5 Amendments to the statistical analysis plan

The overall independent eye case classification was retrieved from the imaging database unlike planned in the protocol (see Section 8).

In addition, the details on images' quality issues were not summarized.

Furthermore, since for PV purposes, data are captured on a case level rather than eye case level and a case possibly involving several events not necessarily assessed in a same way by the reporter as per central review, and due to the lack of standardized data collection and entry, the patient characteristics have been limited to age, gender and country. Subsequently, reference to continuous variables or further variables captured as part of the pharmacovigilance activity is therefore not applicable for this report.

Finally, the following further analyses were added:

- combination of imaging modalities were described;
- anatomical location in relation to the macula were further characterized and involvement described in terms of macula, mid-periphery and periphery alone but also in possible combinations.

## 9.10 Quality control

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

Patient identifiers were removed from images before they were sent to the reading centre. All images were checked for correct labelling corresponding to that in the Novartis Patient Safety database. When duplication or any other discrepancies were identified, they were corrected, so that only images from the treated and affected eye were graded.

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

The SOPs related to programming activities were followed.

# 10 Results

Appendix 1-Listing 1-1 displays all the parameters, locations and results assessed by the reading center for each imaging modality including the cases with visit beyond visit 1 information.

The images collected and obtained at the time of the occurrence (Visit 1) for the treated and affected eyes were evaluated by the reading center and are included in the analyses below.

In the below, the following terms will be used interchangeably: “IOI” and “Posterior segment IOI”; “RO only” and “Retinal vascular occlusion (RO) only”. The term “case” will refer to eye case, the term image will be used to designate image modality.

The results below need to be interpreted within this following context. Majority of inflammatory AEs reported to Novartis in the post-marketing setting was IOI. However, images were requested only from patients with RV/RO. Even amongst this population, images were not provided in all cases. All images were accepted, i.e. there was no standardization of images and not all imaging modalities were accessible. Peripheral and mid-peripheral retinal images were not available for all cases.

Images were requested from patients with reports of RV and/or RO from Feb-2020 to 31-Jan-2021; and for few IOI cases, images were also provided.

## 10.1 Participants

The participants included cases of RV and/or RO c reported to Novartis Patient Safety following brolucizumab use in routine clinical practice for which images were provided to Novartis and read by the Reading Centre.

The unit of observation for this study result is referred to as “eye case” instead of the term “participants”, as the images from each affected and treated eye was assessed independently.

### 10.1.1 Image quality and gradable images

Overall, 484 image modalities at time of event for 231 treated and affected eye cases were reviewed by the reading center (Table 10-1). Note that a single eye case could have several images reported, therefore the total number of images is higher than the number of eye cases.

Quality concerns were reported for 9 images (i.e. all items assessed on that image were marked as "non-gradable"); no overall quality issues were observed for the remaining 475 images.

Overall 9 eye cases were found to be "Not assessable" (i.e. not gradable) (Appendix 1-Listing 1-1):

- For 5 eye cases ([redacted]), all images provided were assessed to be with quality concerns;
- For 4 eye cases ([redacted] even though some elements could be assessed on the images, some other were marked with quality concerns leading overall to the case to be classified as "Not assessable"

The remaining 222 eye cases comprised the cohort of interest and were categorized as "gradable images eye case cohort".

Overall, FP was the most commonly used modality (175 images), followed by OCT (167 images), and FA (107 images). Only a small number of ICGA (20 images) and OCTA (15 images) were received.

**Table 10-1 Image quality and gradable images – All images cohort**

| Imaging modality | All<br>n | Quality concern<br>n | No quality concern<br>n |
|---|---|---|---|
| Any modality - n images** | 484 | 9 | 475 |
| Any modality - n eye cases* | 231 | 9 | 222 |
| Fluorescein Angiography (FA) | 107 | 2 | 105 |
| Fundus Photography (FP) | 175 | 3 | 172 |
| Optical Coherence Tomography (OCT) | 167 | 1 | 166 |
| Optical Coherence Tomography Angiography (OCTA) | 15 | 3 | 12 |
| Indocyanine Green Angiography (ICGA) | 20 | 0 | 20 |

* Refers to number of eye cases i.e. "All" is the number of eye cases send to reading center, "Quality concerns" are the cases for which the case classification based on imaging data was "Not assessable".

** At image level, "Quality concern" refers to images for which all of the items were assessed as "non-gradable".

Source: Appendix 1-Table 1-1

## 10.2 Descriptive data

The descriptive data only related to patient level is considered exploratory and is discussed under Section 10.4.6.

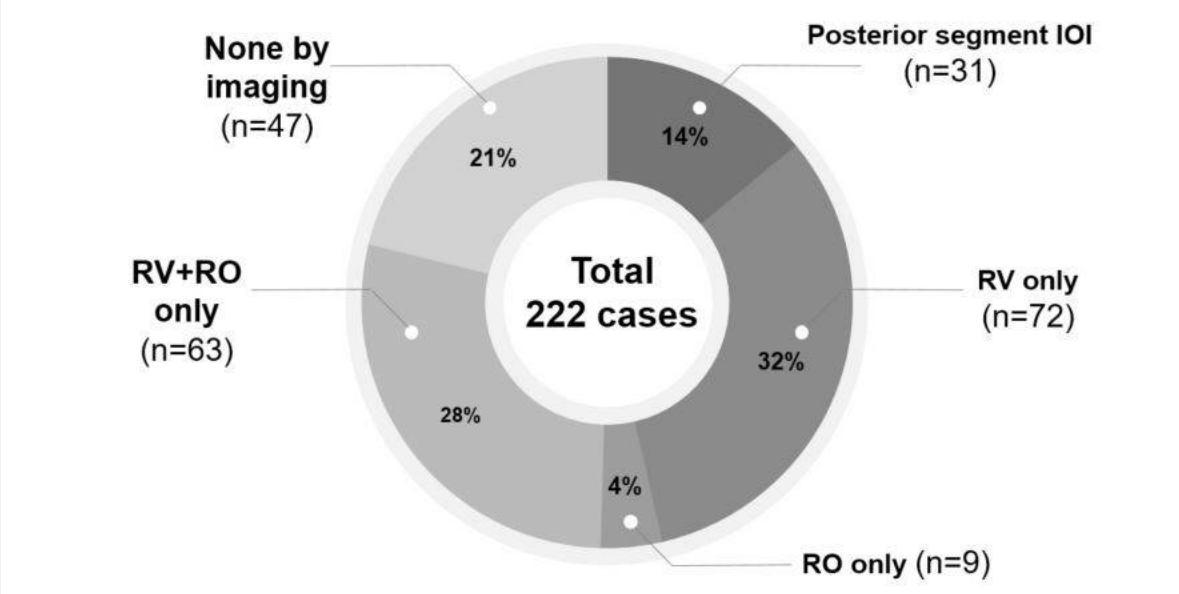
## 10.3 Outcome data

The main outcome was overall eye case classification by the central reader and is discussed under this section. The presence, extent and location of findings based on the imaging data is discussed under main results (Section 10.4).

### Imaging modalities and case classification

Figure 10-1 llustrates the distribution of cases across case classification for the Gradable images eye case cohort.

**Figure 10-1 Reading center case classification**




Note: Only signs of posterior segment segmentation were studied. Thirty-three of the 47 cases classified as "None" by reading center were reported as anterior segment IOI by initial reporter in PV system.
The percentages (%) in the graph are rounded to the nearest whole number, thus the total may not equal 100.
Source: Appendix 1-Table 2-1

Of the 222 assessable eye cases, the majority were classified as RV only (72 cases; 32%), followed by RV+RO only (63 cases; 28%). In total 144 of the 222 eyes (65%) were classified as having RV and/or RO (which was derived combining RV only, RO only, and RV+RO only cases). There were 31 (14%) cases which were classified as having posterior segment IOI only and 47 (21%) were classified as "None" (Figure 10-1). These findings are expected as majority of the images came, by design, from patients who were reported to have RV and/or RO in the PV system. For the cases classified as "None" by Reading Center the majority of them were reported as anterior segment IOI by the HCP (33 cases) (Appendix 1-Listing 1-2).

## 10.4 Main results

### 10.4.1 Imaging modality and reading center case classification

The frequency (n %) of gradable images received at time of event were summarized by imaging modality and reading center case classification as shown in Table 10-2. For RV and/or RO and posterior segment IOI, the majority of gradable images received were FPs (90.3% and 87.1% respectively) followed by OCTs (65.3% and 80.6%, respectively). For the cases classified as "None", the majority of images received were OCTs (93.6%). All images were accepted, i.e. there was no standardization of image type or image acquisition protocol. Also, not all images showed an abnormality.

**Table 10-2 Imaging modality and reading center case classification – Gradable case cohort**

| | Imaging modality n images (%) | | | | |
|---|---|---|---|---|---|
| | **FA** | **FP** | **OCT** | **OCTA** | **ICGA** |
| **Posterior segment IOI N=31** | 9 (29.0) | 27 (87.1) | 25 (80.6) | 2 (6.5) | 5 (16.1) |
| **RV only N=72** | 27 (37.5) | 70 (97.2) | 44 (61.1) | 6 (8.3) | 7 (9.7) |
| **RO only N=9** | 3 (33.3) | 5 (55.6) | 6 (66.7) | 0 | 1 (11.1) |
| **RV+RO only N=63** | 52 (82.5) | 55 (87.3) | 44 (69.8) | 3 (4.8) | 7 (11.1) |
| **RV and/or RO N=144** | 82 (56.9) | 130 (90.3) | 94 (65.3) | 9 (6.3) | 15 (10.4) |
| **None N=47** | 13 (27.7) | 14 (29.8) | 44 (93.6) | 1 (2.1) | 0 |

Row percent presented
Including only images with no quality concerns
Source: Appendix 1-Table 2-1

Most of the cases involved a combination of imaging modalities. The distribution of imaging modality by reading center eye case classification is presented in Table 10-3. Among the 144 eyes with RV and/or RO, the majority had a combination involving FP and OCT (85 cases, 59%) followed by FP and FA (72 cases; 50%).

**Table 10-3 Combined imaging modality and reading center eye case classification – Gradable case cohort**

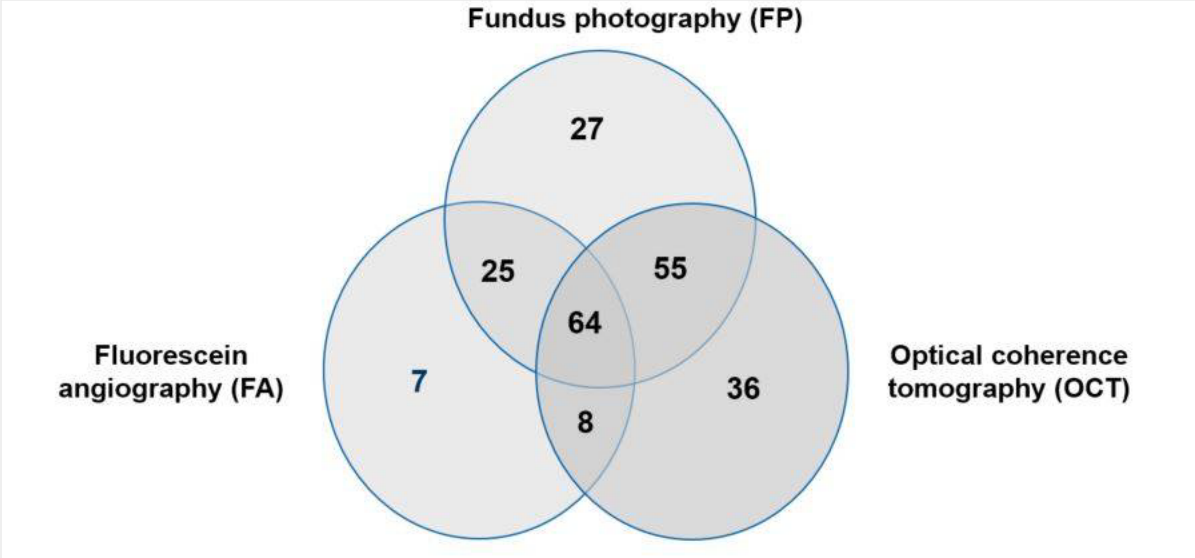
| **Imaging modality combination - n (% )** | **IOI N=31 n (%)** | **RV only N=72 n (%)** | **RO only N=9 n (%)** | **RV+RO only N=63 n (%)** | **RV and/or RO N=144 n (%)** | **None N=47 n (%)** |
|---|---|---|---|---|---|---|
| FA | 0 | 2 (2.8) | 0 | 3 (4.8) | 5 (3.5) | 2 (4.3) |
| FA/FP | 0 | 7 (9.7) | 2 (22.2) | 12 (19.0) | 21 (14.6) | 0 |

| Imaging modality combination - n (% ) | IOI N=31 n (%) | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) | None N=47 n (%) |
|---|---|---|---|---|---|---|
| FA/FP/OCT | 5 (16.1) | 12 (16.7) | 1 (11.1) | 25 (39.7) | 38 (26.4) | 8 (17.0) |
| FA/FP/OCT/OCTA | 0 | 1 (1.4) | 0 | 0 | 1 (0.7) | 0 |
| FA/FP/OCT/OCTA/ICGA | 0 | 1 (1.4) | 0 | 2 (3.2) | 3 (2.1) | 0 |
| FA/FP/OCT/ICGA | 3 (9.7) | 3 (4.2) | 0 | 3 (4.8) | 6 (4.2) | 0 |
| FA/FP/ICGA | 1 (3.2) | 1 (1.4) | 0 | 2 (3.2) | 3 (2.1) | 0 |
| FA/OCT | 0 | 0 | 0 | 5 (7.9) | 5 (3.5) | 3 (6.4) |
| FP | 5 (16.1) | 18 (25.0) | 0 | 2 (3.2) | 20 (13.9) | 1 (2.1) |
| FP/OCT | 10 (32.3) | 21 (29.2) | 1 (11.1) | 8 (12.7) | 30 (20.8) | 4 (8.5) |
| FP/OCT/OCTA | 2 (6.5) | 4 (5.6) | 0 | 1 (1.6) | 5 (3.5) | 1 (2.1) |
| FP/OCT/ICGA | 1 (3.2) | 2 (2.8) | 0 | 0 | 2 (1.4) | 0 |
| FP/ICGA | 0 | 0 | 1 (11.1) | 0 | 1 (0.7) | 0 |
| OCT | 4 (12.9) | 0 | 4 (44.4) | 0 | 4 (2.8) | 28 (59.6) |

Including only images with no quality concerns
Source: Appendix 1-Table 2-3

Figure 10-2 illustrates the combinations of imaging modalities received irrespective of the case classification for gradable images.

**Figure 10-2 Gradable imaging modalities received FA, OCT, and FP images*, alone or in combination (irrespective of eye case classification)**




*OCTA and ICGA images involvement are not displayed here due to the small number of images received; but they are accounted for in the provided counts.
n= number of eye cases involving at least this image modality or combination of modalities
Including only images with no quality concerns
Source: Appendix 1-Table 2-3

### 10.4.2 Common imaging features by image modality

The most common imaging features observed using FA, FP and OCT are discussed under this section. Table 10-4 shows the distributions of images with abnormalities in RV only cases and in the RV and/or RO cases. In RV and/or RO cases, the majority had an abnormality detected on FP (126 cases, 87.5%).

**Table 10-4 Distribution of image with abnormalities by case classification - Gradable image case cohort**

| Imaging modality with abnormalities | RV only N=72 n (%) | RV+RO only N=63 n(%) | RV and/or RO N=144 n (%) |
|---|---|---|---|
| Fundus photography | 67 (93.1) | 54 (85.7) | 126 (87.5) |
| Fluorescein angiography | 24 (33.3) | 52 (82.5) | 79 (54.9) |
| Optical coherence tomography | 16 (22.2) | 30 (47.6) | 52 (36.1) |

Source: Appendix 1-Table 3-1

#### 10.4.2.1 Common imaging features observed on FA

##### 10.4.2.1.1 RV and/or RO eye cases with abnormalities on FA

Among RV and/or RO cases, abnormalities were seen on FA in 79 cases (Table 10-4).

The most common FA features with abnormalities were vascular leakage (71 cases, 89.9%) and retinal arterial occlusion (53 cases; 67.1%) as show in Table 10-5.

**Table 10-5 Imaging features observed in RV and/or RO eye cases with abnormalities on FA**

| FA Grading variables | RV and/or RO N=79 n (%) |
|---|---|
| Vascular leakage | 71 (89.9) |
| Retinal arterial occlusion | 53 (67.1) |
| Retinal ischemia | 46 (58.2) |
| Optic nerve head hyperfluorescence | 43 (54.4) |
| Retinal vessel boxcarring | 9 (11.4) |
| Retinal vein occlusion | 5 (6.3) |
| Choroidal hypoperfusion (early phase) | 3 (3.8) |

% for “Grading variable” = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-3

##### 10.4.2.1.2 RV and RO eye cases with abnormalities on FA

Among RV + RO eye cases, abnormalities were seen on FA in 52 cases (Table 10-4).

Amongst these, retinal arterial occlusion was the most common feature, seen in 50 cases (96.2%), followed by vascular leakage seen in 47 cases (90.4%). (Table 10-6).

**Table 10-6 Imaging features observed on FA with abnormalities in RV and RO cases**

| FA Grading variables | RV + RO only<br>N=52<br>n(%) |
|---|---|
| Retinal arterial occlusion | 50 (96.2) |
| Vascular leakage | 47 (90.4) |
| Retinal ischemia | 43 (82.7) |
| Optic nerve head hyperfluorescence | 31 (59.6) |
| Retinal vessel boxcarring | 9 (17.3) |
| Retinal vein occlusion | 5 (9.6) |
| Choroidal hypoperfusion (early phase) | 3 (5.8) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification
Source: Appendix 1-Table 3-3

#### *10.4.2.1.3* RV eye cases with abnormality on FA

Among RV cases, abnormalities were seen on FA in 24 cases (Table 10-4).

Amongst these, vascular leakage was the most common feature seen in all 24 cases (100%), followed by optic nerve head hyperfluorescence in 11 cases (45.8%) (Table 10-7).

**Table 10-7 Imaging features observed on FA with abnormalities in RV cases**

| FA Grading variables | RV only<br>N=24<br>(%) |
|---|---|
| Vascular leakage | 24 (100) |
| Optic nerve head hyperfluorescence | 11 (45.8) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification
Source: Appendix 1-Table 3-3

### 10.4.2.2 Common imaging features observed on FP

Among RV and/or RO cases, abnormalities were seen on FP in 126 cases (Table 10-4).

Amongst these, the most common features were perivascular sheathing (105 cases, 83.3%). media opacities (58 cases, 46.0%), and retinal hemorrhages (36 cases, 28.6%) (Table 10-8).

**Table 10-8 Imaging features observed on FP with abnormalities in RV and/or RO cases**

| FP Grading variables | RV and/or RO<br>N=126<br>n (%) |
|---|---|
| Perivascular sheathing | 105 (83.3) |
| Media opacities | 58 (46.0) |
| Retinal hemorrhages | 36 (28.6) |

| FP Grading variables | RV and/or RO<br>N=126<br>n (%) |
|---|---|
| Retinal whitening | 29 (23.0) |
| Cotton wool spots | 27 (21.4) |
| Kyrieleis plaques | 19 (15.1) |
| Retinal vessel boxcarring | 3 (2.4) |
| Optic nerve swelling | 2 (1.6) |
| Vitreous hemorrhage | 1 (0.8) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification
Source: Appendix 1-Table 3-3

#### 10.4.2.3 Common imaging features observed on OCT

Among RV and/or RO cases, abnormalities were seen on OCT in 52 cases (Table 10-4).

Amongst these, the most common features were hyperreflective dots in vitreous (33 cases, 63.5%), inner retinal layer hyperreflectivity (19 cases, 36.5%), and paracentral acute middle maculopathy (12 cases, 23.1%) (Table 10-9).

**Table 10-9 Imaging features observed on OCT with abnormalities in RV and/or RO cases**

| OCT Grading variables | RV and/or RO<br>N=52<br>n (%) |
|---|---|
| Hyperreflective dots in vitreous | 33 (63.5) |
| Inner retinal layer hyperreflectivity | 19 (36.5) |
| Paracentral acute middle maculopathy | 12 (23.1) |
| Retinal nerve fiber layer edema around optic nerve | 8 (15.4) |
| Inner retinal thinning | 2 (3.8) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification
Source: Appendix 1-Table 3-3

### 10.4.3 Common imaging features by event type

The grading variables per imaging modality by reading center eye case classification for gradable images case cohort is discussed in this section and is presented in Table 10-10. The percentages presented below take the number of cases with the referred modality as abnormal as reference.

**Table 10-10 Grading variables per imaging modality by reading center eye case classification– Gradable images case cohort**

| Imaging modality/ Grading variables | IOI N=31 n (%) | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) |
|---|---|---|---|---|---|
| **Fluorescein Angiography (FA)** | **1 (3.2)** | **24 (33.3)** | **3 (33.3)** | **52 (82.5)** | **79 (54.9)** |
| Choroidal Hypoperfusion (Early Phase) | 0 | 0 | 0 | 3 (5.8) | 3 (3.8) |
| Optic Nerve Head Hyperfluorescence | 1 (100) | 11 (45.8) | 1 (33.3) | 31 (59.6) | 43 (54.4) |
| Retinal Arterial Occlusion | 0 | 0 | 3 (100) | 50 (96.2) | 53 (67.1) |
| Retinal Ischemia | 1 (100) | 0 | 3 (100) | 43 (82.7) | 46 (58.2) |
| Retinal Neovascularization | 1 (100) | 0 | 0 | 0 | 0 |
| Retinal Vein Occlusion | 0 | 0 | 0 | 5 (9.6) | 5 (6.3) |
| Retinal Vessel Box-carring | 0 | 0 | 0 | 9 (17.3) | 9 (11.4) |
| Vascular Leakage | 0 | 24 (100) | 0 | 47 (90.4) | 71 (89.9) |
| **Fundus Photography (FP)** | **21 (67.7)** | **67 (93.1)** | **5 (55.6)** | **54 (85.7)** | **126 (87.5)** |
| Cotton-Wool Spots | 0 | 14 (20.9) | 0 | 13 (24.1) | 27 (21.4) |
| Kyrieleis Plaques | 0 | 9 (13.4) | 0 | 10 (18.5) | 19 (15.1) |
| Media Opacities | 21 (100) | 29 (43.3) | 3 (60.0) | 26 (48.1) | 58 (46.0) |
| Optic Nerve Swelling | 0 | 1 (1.5) | 0 | 1 (1.9) | 2 (1.6) |
| Perivascular Sheathing | 0 | 59 (88.1) | 0 | 46 (85.2) | 105 (83.3) |
| Retinal Hemorrhages | 0 | 18 (26.9) | 0 | 18 (33.3) | 36 (28.6) |
| Retinal Vessel Box-carring | 0 | 0 | 0 | 3 (5.6) | 3 (2.4) |
| Retinal Whitening | 0 | 8 (11.9) | 3 (60.0) | 18 (33.3) | 29 (23.0) |
| Vitreous Hemorrhage | 0 | 1 (1.5) | 0 | 0 | 1 (0.8) |
| **Optical Coherence Tomography (OCT)** | **22 (71.0)** | **16 (22.2)** | **6 (66.7)** | **30 (47.6)** | **52 (36.1)** |
| Hyperreflective Dots In Vitreous | 22 (100) | 15 (93.8) | 0 | 18 (60.0) | 33 (63.5) |
| Inner Retinal Layer Hyperreflectivity | 0 | 0 | 5 (83.3) | 14 (46.7) | 19 (36.5) |
| Inner Retinal Thinning | 0 | 0 | 2 (33.3) | 0 | 2 (3.8) |
| Paracentral Acute Middle Maculopathy | 0 | 1 (6.3) | 1 (16.7) | 10 (33.3) | 12 (23.1) |
| Retinal Nerve Fiber Layer Edema Around Optic Nerve | 0 | 0 | 2 (33.3) | 6 (20.0) | 8 (15.4) |
| **Optical Coherence Tomography Angiography (OCTA)** | **0** | **2 (2.8)** | **0** | **2 (3.2)** | **4 (2.8)** |
| Foveal Avascular Zone Perimeter Irregularity | 0 | 1 (50.0) | 0 | 1 (50.0) | 2 (50.0) |
| Superficial Capillary Plexus Ischemia | 0 | 1 (50.0) | 0 | 2 (100) | 3 (75.0) |

| Imaging modality/ Grading variables | IOI N=31 n (%) | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) |
|---|---|---|---|---|---|
| **Indocyanine Green Angiography (ICGA)** | **0** | **2 (2.8)** | **1 (11.1)** | **5 (7.9)** | **8 (5.6)** |
| Choroidal Hypocyanescent Areas | 0 | 2 (100) | 1 (100) | 3 (60.0) | 6 (75.0) |
| Early Choroidal Vessel Hypercyanescence | 0 | 0 | 0 | 2 (40.0) | 2 (25.0) |

- % for modality = number of eye cases with this modality / total number of eye case per independent classification
- % for "Grading variable" = number of images with Grading variable / total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-3

### 10.4.3.1 RV only imaging features

The most common features of RV seen on FP (n=67) were perivascular sheathing in 59 cases (88.1%) and media opacities in 29 cases (43.3%). On FA (n=24), vascular leakage was seen in all 24 cases, and optic nerve head hyperfluorescence was observed in 11 cases (45.8%); no other features were observed in this group. On OCT (n=16), the most common feature was hyperreflective dots in vitreous, observed in 15 cases (93.8%).

### 10.4.3.2 RO only imaging features

There were 9 cases in total that were classified as RO only without RV. On FP (n=5), media opacities and retinal whitening were observed in 3 cases each; no other features were observed in this group. In the remaining 6 cases, concomitant signs of inflammation could not be ruled out either due to inability to grade those parameters or lack of availability of images.

Among those with an abnormality on FA (n=3), retinal arterial occlusion and retinal ischemia were seen in 3 cases each; on OCT (n=6) inner retinal layer hyper reflectivity was seen in 5 cases.

### 10.4.3.3 RV+RO only imaging features

The most common features of RV+RO only observed on FA (n=52) were retinal arterial occlusion in 50 cases (96.2%), vascular leakage in 47 cases (90.4%), retinal ischemia in 43 cases (82.7%), and optic nerve head hyperfluorescence in 31 cases (59.6%). On FP (n=54), the most common features were perivascular sheathing in 46 cases (85.2%) and media opacities in 26 cases (48.1%). On abnormal OCT (n=30), hyperreflective dots in vitreous was observed in 18 cases (60.0%), inner retinal layer hyperreflectivity in 14 cases (46.7%), and paracentral acute middle maculopathy in 10 (33.3%).

#### 10.4.3.4 IOI imaging features

The most common imaging features observed in IOI patients with > 1 eye case, was hyperreflective dots in vitreous in all 22 cases assessed by OCT, and media opacities in all 21 cases assessed by FP.

### 10.4.4 Macular involvement

#### 10.4.4.1 Anatomical location in relation to macula

In order to characterize the anatomical locations in relation to the macula a further classification was considered, in which the cases were classified in mutually exclusive regions (involving macula, periphery, and mid-periphery, and any combination of these regions) as presented in Table 10-11.

In the RV and/or RO cases, the largest proportion of cases (44 cases, 30.6%) involved all 3 regions (macula, mid-periphery, and periphery), followed by the macula only (41 cases, 28.5%) and the macula and mid-periphery (37 cases, 25.7%). No macular involvement was reported in 20 cases (13.9%). Note however that wide-field imaging is required in order to detect mid-peripheral and peripheral involvement in cases not involving the macula; which was not necessarily available for all cases.

**Table 10-11 Anatomical location in relation to the macula (alone vs. combined) by reading center eye case classification - Gradable case cohort**

| Anatomical location in relation to macula | IOI N=31 n (%) | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) |
|---|---|---|---|---|---|
| Macula + Mid-Periphery + Periphery | 1 (3.2) | 16 (22.2) | 0 | 28 (44.4) | 44 (30.6) |
| Macula only | 21 (67.7) | 21 (29.2) | 8 (88.9) | 12 (19.0) | 41 (28.5) |
| Macula + Mid-Periphery | 0 | 16 (22.2) | 1 (11.1) | 20 (31.7) | 37 (25.7) |
| Mid-Periphery only | 0 | 11 (15.3) | 0 | 1 (1.6) | 12 (8.3) |
| Mid-Periphery + Periphery | 0 | 5 (6.9) | 0 | 2 (3.2) | 7 (4.9) |
| Periphery only | 0 | 1 (1.4) | 0 | 0 | 1 (0.7) |

Source: Appendix 1-Table 4-3

#### 10.4.4.2 Most common features seen in macula

As per Appendix 1-Table 4-1 (post text table), the macula was affected in the largest proportion of cases regardless of classification, followed by mid-periphery and periphery.

Table 10-12 shows the most common features involving the macula. Note that the involvement mentioned here may include patients that also had mid-peripheral and peripheral involvement as further described in Section 10.4.4.1.

Among RV and/or RO cases, 122 cases (84.7%) were reported with macular involvement. Among these, the most common features observed were perivascular sheathing in 68 cases (55.7%), followed by vascular leakage in 52 cases (42.6%) (Table 10-12).

**Table 10-12 Macula involvement and anatomical location- Gradable case cohort**

| Anatomical location/Location detail | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) |
|---|---|---|---|---|
| **Macula** | **53 (73.6)** | **9 (100)** | **60 (95.2)** | **122 (84.7)** |
| Perivascular sheathing | 31 (58.5) | 0 | 37 (61.7) | 68 (55.7) |
| Vascular leakage | 14 (26.4) | 0 | 38 (63.3) | 52 (42.6) |
| Retinal arterial occlusion | 0 | 3 (33.3) | 36 (60.0) | 39 (32.0) |
| Hyperreflective dots in vitreous | 15 (28.3) | 0 | 18 (30.0) | 33 (27.0) |
| Retinal whitening | 7 (13.2) | 3 (33.3) | 18 (30.0) | 28 (23.0) |
| Cotton wool spots | 13 (24.5) | 0 | 13 (21.7) | 26 (21.3) |
| Retinal ischemia | 0 | 2 (22.2) | 22 (36.7) | 24 (19.7) |
| Retinal hemorrhages | 9 (17.0) | 0 | 14 (23.3) | 23 (18.9) |
| Inner retinal layer hyperreflectivity | 0 | 5 (55.6) | 14 (23.3) | 19 (15.6) |
| Kyrieleis plaques | 7 (13.2) | 0 | 7 (11.7) | 14 (11.5) |
| Paracentral acute middle maculopathy | 1 (1.9) | 1 (11.1) | 10 (16.7) | 12 (9.8) |
| Retinal vessel boxcarring | 0 | 0 | 9 (15.0) | 9 (7.4) |
| Retinal nerve fiber layer edema around optic nerve | 0 | 2 (22.2) | 6 (10.0) | 8 (6.6) |
| Choroidal hypocyanescent areas | 0 | 1 (11.1) | 2 (3.3) | 3 (2.5) |
| Retinal vein occlusion | 0 | 0 | 3 (5.0) | 3 (2.5) |
| Superficial capillary plexus ischemia | 1 (1.9) | 0 | 2 (3.3) | 3 (2.5) |
| Foveal avascular zone perimeter irregularity | 1 (1.9) | 0 | 1 (1.7) | 2 (1.6) |
| Inner retinal thinning | 0 | 2 (22.2) | 0 | 2 (1.6) |

% for anatomical location in relation to macula = number of eye cases with location / total number of eye case per independent classification

% for location detail= number of eye cases with location details / number of eye cases with location per independent classification

Source: Appendix 1-Table 4-1

### 10.4.4.3 Imaging features seen for cases without macular involvement

Features that were seen only in the mid-periphery and periphery are included in Table 10-13. Perivascular sheathing on FP and vascular sheathing on FA were the most common features seen in these regions.

**Table 10-13 Imaging features seen without macular involvement - Gradable case cohort**

| Anatomical location in relation to macula/ Location detail | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) |
|---|---|---|---|---|
| **Mid-periphery only** | **11 (15.3)** | **0** | **1 (1.6)** | **12 (8.3)** |
| Perivascular sheathing | 9 (81.8) | 0 | 0 | 9 (75.0) |
| Cotton-wool spots | 1 (9.1) | 0 | 0 | 1 (8.3) |
| Retinal hemorrhages | 1 (9.1) | 0 | 0 | 1 (8.3) |
| Retinal ischemia | 0 | 0 | 1 (100.0) | 1 (8.3) |
| Retinal whitening | 1 (9.1) | 0 | 0 | 1 (8.3) |
| Vascular leakage | 3 (27.3) | 0 | 1 (100.0) | 4 (33.3) |
| **Mid-periphery + Periphery** | **5 (6.9)** | **0** | **2 (3.2)** | **7 (4.9)** |
| Perivascular sheathing | 5 (100.0) | 0 | 1 (50.0) | 6 (85.7) |
| Choroidal hypocyanescent areas | 1 (20.0) | 0 | 1 (50.0) | 2 (28.6) |
| Retinal hemorrhages | 1 (20.0) | 0 | 1 (50.0) | 2 (28.6) |
| Retinal ischemia | 0 | 0 | 2 (100.0) | 2 (28.6) |
| Vascular leakage | 3 (60.0) | 0 | 2 (100.0) | 5 (71.4) |
| **Periphery only** | **1 (1.4)** | **0** | **0** | **1 (0.7)** |
| Vascular leakage | 1 (100.0) | 0 | 0 | 1 (100.0) |

% for anatomical location in relation to macula = number of eye cases with location / total number of eye case per independent classification

% for location detail= number of eye cases with location details / number of eye cases with location per independent classification

Source: Appendix 1-Table 4-5

### 10.4.5 Distribution of imaging features by location, extent and presence

The eye cases distribution per anatomical location are presented in Table 10-14. In RV only eye cases, retina was affected in 71 of 72 cases (98.6%). Vascular involvement was observed in 68 cases (94.4%); arteries were involved more than veins with 57 cases (79.2%) (including arterial only and both arterial and vein cases; 54 and 3 cases respectively).

In RV and/or RO eye cases, retina was affected in 142 of 144 cases (98.6%), vascular involvement was observed in 139 cases (96.5%). Arterial involvement was seen in 120 (83.3%); ischemia in 62 cases (43.1%), and vascular leakage in 71 cases (49.3%). The vitreous was involved in 73 cases (50.7%).

**Table 10-14 Anatomical location and sub-location by reading center classification - Gradable case cohort**

| Anatomical location / sub-location | IOI N=31 n (%) | RV only N=72 n (%) | RO only N=9 n (%) | RV+RO only N=63 n (%) | RV and/or RO N=144 n (%) |
|---|---|---|---|---|---|
| **Retina** | 1 (3.2) | 71 (98.6) | 8 (88.9) | 63 (100) | 142 (98.6) |
| Vascular | 1 (3.2) | 68 (94.4) | 8 (88.9) | 63 (100) | 139 (96.5) |
| Arterial only | 0 | 54 (75.0) | 3 (33.3) | 53 (84.1) | 110 (76.4) |
| Vein only | 0 | 2 (2.8) | 0 | 1 (1.6) | 3 (2.1) |
| Both arterial and vein | 0 | 3 (4.2) | 0 | 7 (11.1) | 10 (6.9) |
| Ischemia | 1 (3.2) | 2 (2.8) | 8 (88.9) | 52 (82.5) | 62 (43.1) |
| Vascular leakage | 0 | 24 (33.3) | 0 | 47 (74.6) | 71 (49.3) |
| General retina | 0 | 36 (50.0) | 3 (33.3) | 36 (57.1) | 75 (52.1) |
| Vitreous | 31 (100) | 35 (48.6) | 3 (33.3) | 35 (55.6) | 73 (50.7) |
| Choroid | 0 | 2 (2.8) | 1 (11.1) | 8 (12.7) | 11 (7.6) |
| Optic nerve | 1 (3.2) | 12 (16.7) | 3 (33.3) | 35 (55.6) | 50 (34.7) |

The percentages are based on 'N'.
Source: Appendix 1-Table 3-1

### 10.4.5.1 Occlusion types

A summary of occlusion type is presented in Table 10-15. In RV+RO only (n=63), the most common location of occlusion was branch (28 cases, 44.4%), followed by peripheral (15 cases, 23.8%) and central (9 cases, 14.3%). The majority of cases involved arterial occlusion regardless of location; however there were 5 cases that also had venous occlusion (post text Appendix 1-Table 3-3). Multiple occlusions were noted in 37 of the 50 cases of RV + RO cases, in whom a retinal arterial occlusion was detected (post text Appendix 1-Table 6-1).

**Table 10-15 Occlusion type by reading center eye case classification – Gradable case cohort**

| Occlusion type/ Location detail | RO only N=9 n (%) | RV+RO only N=63 n (%) |
|---|---|---|
| **Central** | **1 (11.1)** | **9 (14.3)** |
| Retinal Arterial Occlusion | 1 (100) | 9 (100) |
| **Branch** | **2 (22.2)** | **28 (44.4)** |
| Retinal Arterial Occlusion | 2 (100) | 27 (96.4) |
| Retinal Vein Occlusion | 0 | 3 (10.7) |
| **Peripheral** | **0** | **15 (23.8)** |
| Retinal Arterial Occlusion | 0 | 13 (86.7) |
| Retinal Vein Occlusion | 0 | 2 (13.3) |

% for occlusion type = number of eye cases with occlusion type / total number of eye case per independent classification

% for location detail= number of eye cases with location details / number of eye cases with occlusion type per independent classification
Source: Appendix 1-Table 5-1

#### 10.4.5.1.1 Retinal arterial and vein occlusion

Extent and location of retinal arterial and vein occlusion are presented in Table 10-16 for cases with arterial and vein involvement.

For RV and RO cases, the retinal occlusion was mainly branch than central; peripheral vessels were involved in about 1/4th of cases and multiple vessels more likely than single. Occlusions were mainly arterial (53 cases), however there were 5 cases that also had venous occlusion (Appendix 1-Listing 1-1).

**Table 10-16 Retinal arterial and vein occlusion in cases with arterial and vein involvement: Extent and location**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Arterial** | **N=57** | **N=3** | **N=60** | **N=120** |
| **Retinal Arterial Occlusion n (%)** | **0** | **3 (100)** | **50 (83)** | **53 (44)** |
| Type | | | | |
| Central | 0 | 1 | 9 | 10 |
| Branch | 0 | 2 | 27 | 29 |
| Peripheral | 0 | 0 | 13 | 13 |
| Number | | | | |
| Single | 0 | 3 | 11 | 14 |
| Multiple | 0 | 0 | 37 | 37 |
| **Vein** | **N=5** | **N=0** | **N=8** | **N=13** |
| **Retinal Vein Occlusion n (%)** | **0** | **0** | **5 (63)** | **5 (38)** |
| Type | | | | |
| Branch | 0 | 0 | 3 | 3 |
| Peripheral | 0 | 0 | 2 | 2 |
| Number | | | | |
| Single | 0 | 0 | 2 | 2 |
| Multiple | 0 | 0 | 3 | 3 |

The column totals may not add up as not all characteristics were gradable or available.
Source: Appendix 1-Table 6-1

### 10.4.5.2 Other imaging findings

Other anatomical location involved as per the reading center eye classification are described in this section.

#### 10.4.5.2.1 Perivascular Sheathing

Among RV and/or RO cases with perivascular sheathing, 92 cases had only arterial involvement, 3 had only venous involvement and 7 cases had both as shown in Table 10-17. Sheathing was observed in all three areas (macula, mid-periphery and periphery).

**Table 10-17 Extent of involvement- perivascular sheathing**

| Location | RV and/or RO |
|---|---|
| **Arterial** | **N=120** |
| **Perivascular sheathing n (%)** | **99 (83%)** |
| Vessel type | |
| Artery | 92 |
| Both | 7 |
| Location | |
| Macula | 66 |
| Mid-periphery | 63 |
| Periphery | 24 |
| Extent | |
| Sectoral | 65 |
| Diffuse | 33 |
| **Vein** | **N=13** |
| **Perivascular sheathing n (%)** | **10 (77%)** |
| Vessel type | |
| Vein | 3 |
| Both | 7 |
| Location | |
| Macula | 5 |
| Mid-periphery | 9 |
| Periphery | 5 |
| Extent | |
| Sectoral | 6 |
| Diffuse | 4 |

The column totals may not add up as not all characteristics were gradable or available.
Source: Appendix 1-Table 6-1

#### 10.4.5.2.2 Boxcarring and Kyrieleis plaques

As per Table 10-18, among RV and/or RO cases with arterial involvement, retinal vessel boxcarring was observed in 12 cases (10%). Majority had macular involvement (9 cases). Kyrieleis plaques were observed in 19 cases (16%) including a majority with macular involvement (14 cases).

**Table 10-18 Extent of involvement - Boxcarring and Kyrieleis plaque**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Arterial** | **N=57** | **N=3** | **N=60** | **N=120** |
| Retinal vessel boxcarring n (%) | 0 | 0 | 12 (20) | 12 (10) |
| Location | | | | |
| Macula | 0 | 0 | 9 | 9 |
| Mid-periphery | 0 | 0 | 2 | 2 |

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| Kyrieleis plaques n (%) | 9 (16) | 0 | 10 (17%) | 19 (16%) |
| Location | | | | |
| Macula | 7 | 0 | 7 | 14 |
| Mid-periphery | 4 | 0 | 4 | 8 |

The column totals may not add up as not all characteristics were gradable or available.
Source: Appendix 1-Table 6-1

#### 10.4.5.2.3 Ischemia

Cases involving ischemia are summarized in Table 10-19. Signs of retinal ischemia on FA were seen in 46 cases with RV and/or RO. Ischemia was seen in all three regions: macula (24 cases), mid-periphery (36 cases), and periphery (23 cases). There were no cases with retinal neovascularization. Inner retinal layer hyper-reflectivity was seen in 19 cases and paracentral acute middle maculopathy (PAMM) was observed in 12 cases with RV and/or RO.

**Table 10-19 Extent of involvement - Ischemia**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Ischemia** | **N=2** | **N=8** | **N=52** | **N=62** |
| Retinal ischemia n (%) | 0 | 3 (38) | 43 (83) | 46 (74) |
| Location | | | | |
| Macula | 0 | 2 | 22 | 24 |
| Mid-periphery | 0 | 1 | 35 | 36 |
| Periphery | 0 | 0 | 23 | 23 |
| Mid-periphery/periphery: extent | | | | |
| Sectoral | 0 | 1 | 21 | 22 |
| Diffuse | 0 | 0 | 16 | 16 |
| Retinal neovascularization n (%) | 0 | 0 | 0 | 0 |
| Superficial capillary plexus ischemia n (%) | 1 (50) | 0 | 2 (3.8) | 3 (4.8) |
| Inner retinal layer hyperreflectivity n (%) | 0 | 5 (63) | 14 (27) | 19 (31) |
| Paracentral acute middle maculopathy n (%) | 1 (50) | 1 (13) | 10 (19) | 12 (19) |
| Inner retinal thinning n (%) | 0 | 2 (25) | 0 | 2 (3.2) |
| Foveal avascular zone perimeter irregularity n (%) | 1 (50) | 0 | 1 (1.9) | 2 (3.2) |

The column totals may not add up as not all characteristics were gradable or available.
Source: Appendix 1-Table 6-1

#### 10.4.5.2.4 Vascular leakage

As per Table 10-20, among the 71 RV and/or RO cases in which vascular leakage was observed, the location was in the macula in 52 cases, in the mid-periphery in 40 cases and in the periphery in 14 cases.

**Table 10-20 Extent of involvement - Vascular leakage**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Vascular leakage** | **N=24** | **N=0** | **N=47** | **N=71** |
| Location | | | | |
| Macula | 14 | 0 | 38 | 52 |
| Mid-periphery | 15 | 0 | 25 | 40 |
| Periphery | 9 | 0 | 5 | 14 |
| Mid-periphery/periphery: extent | | | | |
| Sectoral | 7 | 0 | 13 | 20 |
| Diffuse | 11 | 0 | 11 | 22 |

The column totals may not add up as not all characteristics were gradable or available.
Source: Appendix 1-Table 6-1

#### 10.4.5.2.5 Retinal whitening

As per Table 10-21, retinal whitening was observed in 29 eye cases with RV and/or RO. In the majority of cases it was observed in the macula (28 of 29 cases) and was more sectoral (24 cases) than diffuse (3 cases).

**Table 10-21 Extent of involvement - Retinal whitening**

| | RV only | RO only | RV + RO Oonly | RV and/or RO |
|---|---|---|---|---|
| **Retinal whitening, n** | **8** | **3** | **18** | **29** |
| Location | | | | |
| Macula | 7 | 3 | 18 | 28 |
| Mid-periphery | 2 | 0 | 1 | 3 |
| Periphery | 0 | 0 | 1 | 1 |
| Mid-periphery/periphery: extent | | | | |
| Sectoral | 8 | 3 | 13 | 24 |
| Diffuse | 0 | 0 | 3 | 3 |

The column totals may not add up as not all characteristics were gradable or available.
Source: Appendix 1-Table 6-1

#### 10.4.5.2.6 Retinal hemorrhages

As per Table 10-22, retinal hemorrhages were observed in 36 cases with RV and/or RO. These were mainly observed in the macula (23 cases) and mid peripheral region (22 cases) and were mostly sectoral in extent (18 cases). Majority of cases had small hemorrhages (28 cases) with 1 case having a large hemorrhage. The pattern was scattered in majority (20 cases). Majority of hemorrhages were pre-retinal (15 cases) or dot blot hemorrhages (15 cases).

**Table 10-22 Extent of involvement - Retinal hemorrhages**

| | RV only | RO only | RV and RO only | RV and/or RO |
|---|---|---|---|---|
| **Retinal hemorrhages, n** | **18** | **0** | **18** | **36** |

| | RV only | RO only | RV and RO only | RV and/or RO |
|---|---|---|---|---|
| Location | | | | |
| Macula | 9 | 0 | 14 | 23 |
| Mid-periphery | 10 | 0 | 12 | 22 |
| Periphery | 7 | 0 | 5 | 12 |
| Mid-periphery/periphery: extent | | | | |
| Sectoral | 9 | 0 | 9 | 18 |
| Diffuse | 4 | 0 | 3 | 7 |
| Size | | | | |
| Large | 0 | 0 | 1 | 1 |
| Small | 14 | 0 | 14 | 28 |
| Mixed | 3 | 0 | 3 | 6 |
| Pattern | | | | |
| Scattered | 13 | 0 | 7 | 20 |
| Confluent | 0 | 0 | 4 | 4 |
| Perivenular | 5 | 0 | 7 | 12 |
| Type | | | | |
| Pre retinal | 9 | 0 | 6 | 15 |
| Flame | 0 | 0 | 1 | 1 |
| Dot blot | 7 | 0 | 8 | 15 |
| Sub retinal | 1 | 0 | 0 | 1 |

Source: Appendix 1-Table 6-1

#### 10.4.5.2.7 Cotton wool spots and cystoid macula edema

As per Table 10-23, no eye cases of cystoid macular edema were observed.

Among the 27 eye cases of RV and/or RO in which cotton wool spots were observed, the location was mainly in the macula (26 cases), extent was mainly sectoral (23 cases), and all had a scattered pattern (27 cases).

**Table 10-23 Extent of involvement - Cotton wool spots and cystoid macula edema**

| | RV only | RV + RO only | RV and/or RO |
|---|---|---|---|
| **Cotton wool spots, n** | **14** | **13** | **27** |
| Location | | | |
| Macula | 13 | 13 | 26 |
| Mid-periphery | 1 | 2 | 3 |
| Extent | | | |
| Sectoral | 12 | 11 | 23 |
| Diffuse | 2 | 2 | 4 |
| Pattern | | | |
| Scattered | 14 | 13 | 27 |
| **Cystoid macula edema n** | **0** | **0** | **0** |

Source: Appendix 1-Table 6-1

#### 10.4.5.2.8 Vitreous involvement

As per Table 10-24, of the 73 eye cases with RV and/or RO with vitreous involvement, 58 cases (79%) had media opacities on FP, and 33 cases had hyperreflective dots (45%) on OCT. Only 1 case of vitreous hemorrhage was observed (1.4%).

**Table 10-24 Extent of involvement - Vitreous**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Vitreous** | **N=35** | **N=3** | **N=35** | **N=73** |
| Media opacities n (%) | 29 (83) | 3 (100) | 26 (74) | 58 (79) |
| Vitreous hemorrhage n (%) | 1 (2.9) | 0 | 0 | 1 (1.4) |
| Hyperreflective dots in vitreous n (%) | 15 (43) | 0 | 18 (51) | 33 (45) |

Source: Appendix 1-Table 6-1

#### 10.4.5.2.9 Choroidal involvement

Eleven (7.6%) of the 144 eye cases with RV and/or RO had choroidal involvement (Table 10-25). Among these, choroidal hypocyanescent areas were observed on ICGA in 6 cases and early phase choroidal hypoperfusion was observed on FA in 3 cases.

**Table 10-25 Extent of involvement- Choroid**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Choroid** | **N=2** | **N=1** | **N=8** | **N=11** |
| Choroidal hypoperfusion (early phase) n (%) | 0 | 0 | 3 (38) | 3 (27) |
| Early choroidal vessel hypercyanescence n (%) | 0 | 0 | 2 (25) | 2 (18) |
| Choroidal hypocyanescent areas n (%) | 2 (100) | 1 (100) | 3 (38) | 6 (55) |
| Pattern | | | | |
| Discrete spots | 2 | 1 | 2 | 5 |
| Geographic | 0 | 0 | 1 | 1 |
| Time frame | | | | |
| Late | 1 | 0 | 1 | 2 |
| Mid | 0 | 1 | 1 | 2 |
| Location | | | | |
| Macula | 0 | 1 | 2 | 3 |
| Mid-periphery | 2 | 0 | 2 | 4 |
| Periphery | 1 | 0 | 0 | 1 |

Source: Appendix 1-Table 6-1

#### 10.4.5.2.10 Optic nerve involvement

Fifty (34.7%) of the 144 eye cases with RV and/or RO had optic nerve head involvement (Table 10-26). Among these, on FA, 43 cases (86%) had optical nerve head hyperfluorescence.

Other findings included retinal nerve fiber layer edema around optic nerve on OCT in 8 cases (16%), and optic nerve swelling on FP in 2 cases (4%).

**Table 10-26 Optic nerve involvement**

| | RV only | RO only | RV + RO only | RV and/or RO |
|---|---|---|---|---|
| **Optic nerve** | **N=12** | **N=3** | **N=35** | **N=50** |
| Optic nerve head hyperfluorescence n (%) | 11 (92) | 1 (33) | 31 (89) | 43 (86) |
| Time frame | | | | |
| Early | 0 | 0 | 3 | 3 |
| Late | 4 | 0 | 8 | 12 |
| Type | | | | |
| Leak | 3 | 0 | 6 | 9 |
| Stain | 1 | 0 | 5 | 6 |
| Optic nerve swelling n(%) | 1 (8.3) | 0 | 1 (2.9) | 2 (4.0) |
| Retinal nerve fiber layer edema around optic nerve n (%) | 0 | 2 (67) | 6 (17) | 8 (16) |

Source: Appendix 1-Table 6-1

### 10.4.6 Exploratory objectives: Patient demographics

Demographic information is presented at patient level rather than eye cases level under the worse eye case classification for patient with bilateral events in Table 10-27. Events were mainly seen in patients 70 years of age or older. Cases were reported mostly in females (103 of 198, 52%), compared to males (90 of 198, 45%); gender was missing for 3% of the cases (5 of 198). Most of the cases of RV and/or RO were reported from Japan (50%) and the United States (41%).

**Table 10-27 Patient characteristics – Gradable images case cohort**

| | IOI N=31 n (%) | RV only N=65 n (%) | RO only N=8 n (%) | RV+RO only N=60 n (%) | RV and/or RO N=133 n (%) | None N=34 n (%) |
|---|---|---|---|---|---|---|
| **Age - n (%)** | | | | | | |
| 50 - < 60 years | 1 (3) | 1 (2) | 0 (0) | 2 (3) | 3 (2) | 0 (0) |
| 60 - < 70 years | 3 (10) | 14 (22) | 0 (0) | 2 (3) | 16 (12) | 7 (21) |
| 70 - < 80 years | 15 (48) | 23 (35) | 5 (63) | 25 (42) | 53 (40) | 11 (32) |
| ≥ 80 years | 9 (29) | 19 (29) | 3 (38) | 27 (45) | 49 (37) | 8 (24) |
| Adult age unk | 1 (3) | 4 (6) | 0 (0) | 1 (2) | 5 (4) | 5 (15) |
| Elderly age unk | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Missing | 1 (3) | 4 (6) | 0 (0) | 3 (5) | 7 (5) | 3 (9) |
| **Gender - n (%)** | | | | | | |
| Female | 17 (55) | 27 (42) | 5 (63) | 42 (70) | 74 (56) | 12 (35) |
| Male | 14 (45) | 37 (57) | 3 (38) | 17 (28) | 57 (43) | 19 (56) |
| Missing | 0 (0) | 1 (2) | 0 (0) | 1 (2) | 2 (2) | 3 (9) |

| | IOI N=31 n (%) | RV only N=65 n (%) | RO only N=8 n (%) | RV+RO only N=60 n (%) | RV and/or RO N=133 n (%) | None N=34 n (%) |
|---|---|---|---|---|---|---|
| **Country - n (%)** | | | | | | |
| Australia | 2 (6) | 1 (2) | 0 (0) | 0 (0) | 1 (1) | 1 (3) |
| Canada | 1 (3) | 0 (0) | 0 (0) | 1 (2) | 1 (1) | 0 (0) |
| Germany | 1 (3) | 2 (3) | 1 (13) | 2 (3) | 5 (4) | 5 (15) |
| Japan | 23 (74) | 46 (71) | 2 (25) | 18 (30) | 66 (50) | 14 (41) |
| Malaysia | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| Portugal | 1 (3) | 0 (0) | 0 (0) | 2 (3) | 2 (2) | 0 (0) |
| Switzerland | 1 (3) | 1 (2) | 0 (0) | 0 (0) | 1 (1) | 1 (3) |
| United Arab Emirates | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (1) | 0 (0) |
| United States | 2 (6) | 13 (20) | 5 (63) | 37 (62) | 55 (41) | 13 (38) |

Displaying case counts (i.e. patients) rather than eye case.

Cases involving bilateral events are counted under the worse eye classification considering the following hierarchy: None<IOI<RV only<RO only<RV+RO only.

Source: Appendix 1-Table 7-1

## 10.5 Other analyses – Japan subgroup

A subgroup analysis was performed for the Japanese population.

### 10.5.1 Image quality and gradable images - Japan

The image quality for Japan population is presented in Table 10-28. There were 236 images for 108 eye cases. Of these, 5 images were reported to have a quality concern. Three eye cases were classified as “not assessable”; the remaining 105 eye cases comprised the cohort of interest.

**Table 10-28 Image quality and gradable images – All images cohort- Japan**

| | All n | Quality concern n | No quality concern n |
|---|---|---|---|
| Any modality - n images** | 236 | 5 | 231 |
| Any modality - n eye cases* | 108 | 3 | 105 |
| Fluorescein Angiography (FA) | 34 | 0 | 34 |
| Fundus Photography (FP) | 95 | 2 | 93 |
| Optical Coherence Tomography (OCT) | 77 | 1 | 76 |
| Optical Coherence Tomography Angiography (OCTA) | 14 | 2 | 12 |
| Indocyanine Green Angiography (ICGA) | 16 | 0 | 16 |

* Refers to number of eye cases i.e. "All" is the number of eye cases send to reading center, "Quality concerns" are the cases for which the case classification based on imaging data was "Not assessable".

** At image level, "Quality concern" refers to images for which all of the items were assessed as "non-gradable".

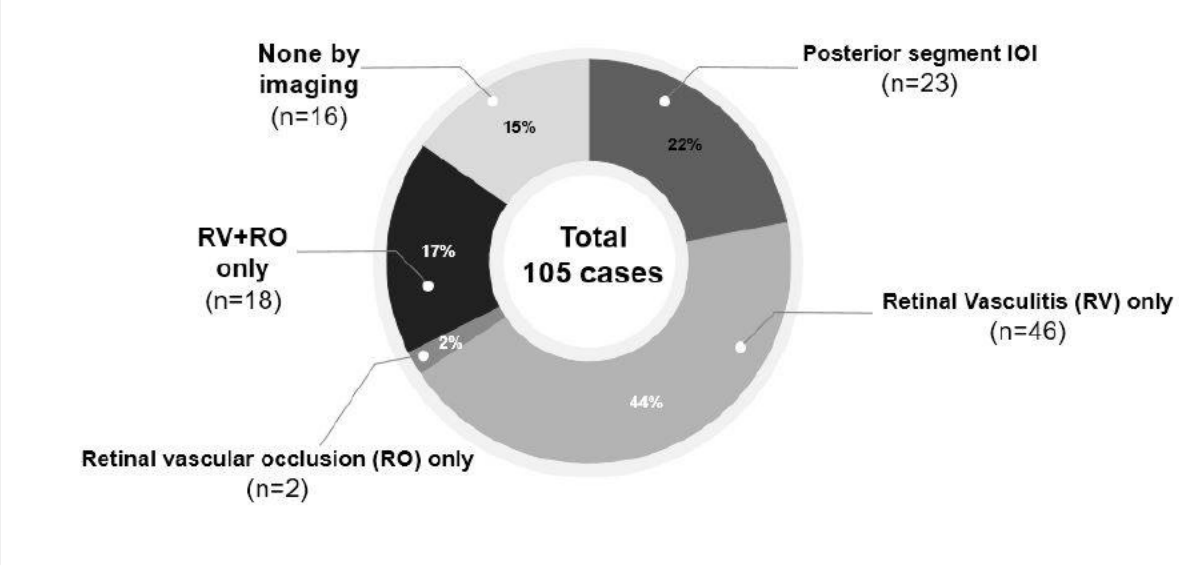
Source: Appendix 1-Table 1-2

### 10.5.2 Imaging modalities and case classification - Japan

The imaging modality and reading center case classification is presented for Japan population in Table 10-29.

Of the 105 assessable eye cases, the majority were classified as RV only (46, 44%), followed by posterior segment IOI (23 cases, 22%) and RV and RO (18 cases, 17%). Figure 10-3 illustrates the distribution of cases across case classification for the Gradable images eye case cohort for Japan.

**Figure 10-3 Reading center case classification - Japan**




Source: Appendix 1-Table 2-2

**Table 10-29 Imaging modality and reading center case classification – Gradable case cohort – Japan**

| | Imaging modality n images (%) | | | | |
|---|---|---|---|---|---|
| **Imaging modality – n (%)** | **FA** | **FP** | **OCT** | **OCTA** | **ICGA** |
| **Posterior segment IOI N=23** | 6 (26.1) | 21 (91.3) | 18 (78.3) | 2 (8.7) | 4 (17.4) |
| **RV only N=46** | 11 (23.9) | 46 (100) | 30 (65.2) | 6 (13.0) | 5 (10.9) |
| **RO only N=2** | 1 (50.0) | 2 (100) | 0 | 0 | 1 (50.0) |
| **RV+RO only N=18** | 11 (61.1) | 17 (94.4) | 14 (77.8) | 3 (16.7) | 6 (33.3) |
| **RV and/or RO N=66** | 23 (34.8) | 65 (98.5) | 44 (66.7) | 9 (13.6) | 12 (18.2) |
| **None N=16** | 4 (25.0) | 7 (43.8) | 14 (87.5) | 1 (6.3) | 0 |

Includes only images with no quality concerns
Source: Appendix 1-Table 2-2

Most of the cases had combination of imaging modalities. The distribution of imaging modality by reading center eye case classification is presented in Table 10-30. Among the 66 eyes with RV and/or RO, the largest proportion had a combination of FP and OCT (23 cases, 34.8%).

**Table 10-30 Combined imaging modality and reading center eye case classification – Gradable case cohort – Japan**

| Imaging modality - n (% ) | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) | None N=16 n (%) |
|---|---|---|---|---|---|---|
| FA | 0 | 0 | 0 | 0 | 0 | 1 (6.3) |
| FA/FP | 0 | 4 (8.7) | 1 (50.0) | 1 (5.6) | 6 (9.1) | 0 |
| FA/FP/OCT | 2 (8.7) | 3 (6.5) | 0 | 3 (16.7) | 6 (9.1) | 3 (18.8) |
| FA/FP/OCT/OCTA | 0 | 1 (2.2) | 0 | 0 | 1 (1.5) | 0 |
| FA/FP/OCT/OCTA/ICGA | 0 | 1 (2.2) | 0 | 2 (11.1) | 3 (4.5) | 0 |
| FA/FP/OCT/ICGA | 3 (13.0) | 1 (2.2) | 0 | 2 (11.1) | 3 (4.5) | 0 |
| FA/FP/ICGA | 1 (4.3) | 1 (2.2) | 0 | 2 (11.1) | 3 (4.5) | 0 |
| FA/OCT | 0 | 0 | 0 | 1 (5.6) | 1 (1.5) | 0 |
| FP | 4 (17.4) | 11 (23.9) | 0 | 1 (5.6) | 12 (18.2) | 1 (6.3) |
| FP/OCT | 9 (39.1) | 18 (39.1) | 0 | 5 (27.8) | 23 (34.8) | 2 (12.5) |
| FP/OCT/OCTA | 2 (8.7) | 4 (8.7) | 0 | 1 (5.6) | 5 (7.6) | 1 (6.3) |
| FP/OCT/ICGA | 0 | 2 (4.3) | 0 | 0 | 2 (3.0) | 0 |
| FP/ICGA | 0 | 0 | 1 (50.0) | 0 | 1 (1.5) | 0 |
| OCT | 2 (8.7) | 0 | 0 | 0 | 0 | 8 (50.0) |

Source: Appendix 1-Table 2-4

### 10.5.2.1 Common imaging features by imaging modality – Japan

The most common imaging features observed with FA, FP OCT, ICGA, and OCTA are discussed. Table 10-31 shows the distributions of images with abnormalities in RV only cases and in the RV and/or RO cases. In RV and/or RO cases, majority had an abnormality detected on FP (63 cases, 95.5%), on FA (23 cases, 34.8%), on OCT (22 cases, 33.3%), OCTA (4 cases, 6.1%), and ICGA (7 cases, 10.6%). Note however that OCTA and ICGA were not frequently used image modalities (Table 10-29).

**Table 10-31 Distribution of images with abnormalities by case classification - Gradable image case cohort – Japan**

| Imaging modality with abnormalities | RV only N=46 n (%) | RV and/or RO N=66 n(%) |
|---|---|---|
| FP | 44 (95.7) | 63 (95.5) |
| FA | 11 (23.9) | 23 (34.8) |
| OCT | 13 (28.3) | 22 (33.3) |

| Imaging modality with abnormalities | RV only N=46 n (%) | RV and/or RO N=66 n(%) |
|---|---|---|
| OCTA | 2 ( 4.3) | 4 (6.1) |
| ICGA | 2 ( 4.3) | 7 (10.6) |

Source: Appendix 1-Table 3-2

#### 10.5.2.1.1 Common imaging features observed in FA - Japan

### RV and/or RO eye cases with abnormalities on FA

Among RV and/or RO cases, abnormalities were seen on FA in 23 cases (Table 10-31). Among these, the most common abnormalities were vascular leakage (20 cases, 87.0%), followed by retinal arterial occlusion and optic nerve head hyperfluorescence (10 cases, 43.5% each) (Table 10-32).

**Table 10-32 Imaging features observed on FA with abnormalities in RV and/or RO eye cases –– Japan**

| FA Grading variables | RV and/or RO N=23 n (%) |
|---|---|
| Vascular leakage | 20 (87.0) |
| Retinal arterial occlusion | 10 (43.5) |
| Optic nerve head hyperfluorescence | 10 (43.5) |
| Retinal ischemia | 7 (30.4) |
| Retinal vessel boxcarring | 2 (8.7) |
| Retinal vein occlusion | 2 (8.7) |

% for “Grading variable” = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-4

### RV eye cases with abnormalities on FA

Among RV cases, abnormalities were seen on FA in 11 cases (Table 10-31).

Amongst these, the features observed were vascular leakage in all 11 cases (100%), and Optic Nerve head hyperfluorescence in 6 cases (54.5%) (Table 10-33).

**Table 10-33 Imaging features observed on FA with abnormalities - in RV eye cases – Japan**

| FA Grading variables | RV only N=11 n (%) |
|---|---|
| Vascular leakage | 11 (100) |
| Optic nerve head hyperfluorescence | 6 (54.5) |

% for “Grading variable” = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-4

### RV and RO only eye cases with abnormalities on FA

Among RV+RO cases, abnormalities were seen on FA in 11 cases (Table 10-31).

Among these, the common FA features with abnormalities were vascular leakage and retinal arterial occlusion (in 9 cases, 81.8% each), followed by retinal ischemia (6 cases, 54.5%) (Table 10-34).

**Table 10-34 Imaging features observed on FA with abnormalities - in RV and RO only eye cases – Japan**

| FA Grading variables | RV + RO only N=11 n (%) |
|---|---|
| Vascular leakage | 9 (81.8) |
| Retinal arterial occlusion | 9 (81.8) |
| Retinal ischemia | 6 (54.5) |
| Optic nerve head hyperfluorescence | 4 (36.4) |
| Retinal vessel boxcarring | 2 (18.2) |
| Retinal vein occlusion | 2 (18.2) |

% for “Grading variable” = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-4

#### 10.5.2.1.2 Common imaging features observed in FP - Japan

Among RV and/or RO cases, abnormalities were seen on FP in 63 cases (Table 10-31).

Among these the most common abnormalities were perivascular sheathing (58 cases, 92.1%), followed by media opacities (30 cases, 47.6%), and retinal hemorrhages (18 cases, 28.6%) (Table 10-35).

**Table 10-35 Imaging features observed on FP with abnormalities in RV and/or RO cases - Japan**

| FP grading variables | RV and/or RO N=63 n (%) |
|---|---|
| Perivascular sheathing | 58 (92.1) |
| Media opacities | 30 (47.6) |
| Retinal hemorrhages | 18 (28.6) |
| Retinal whitening | 14 (22.2) |
| Kyrieleis plaques | 14 (22.2) |
| Cotton wool spots | 13 (20.6) |
| Optic nerve swelling | 1 (1.6) |
| Vitreous hemorrhage | 1 (1.6) |

% for “Grading variable” = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-4

#### 10.5.2.1.3 Common imaging features observed on OCT - Japan

Among RV and/or RO cases, abnormalities were seen on OCT in 22 cases (Table 10-31).

Among these the most common features were hyperreflective dots in vitreous in 20 cases, 90.9% (Table 10-36).

**Table 10-36 Imaging features observed on OCT with abnormalities in RV and/or RO cases - Japan**

| OCT Grading variables | RV and/or RO<br>N=22<br>n (%) |
|---|---|
| Hyperreflective dots in vitreous | 20 (90.9) |
| Inner retinal layer hyperreflectivity | 4 (18.2) |
| Paracentral acute middle maculopathy | 2 (9.1) |
| Retinal nerve fiber layer edema around optic nerve | 3 (13.6) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification
Source: Appendix 1-Table 3-4

#### 10.5.2.1.4 Common imaging features observed on OCTA

Among RV and/or RO cases, abnormalities were seen on OCTA in 4 cases (Table 10-31). These were superficial capillary plexus ischemia (3 cases) and foveal avascular zone perimeter irregularity (2 cases) (Table 10-37).

**Table 10-37 Imaging features observed on OCTA with abnormalities in RV and/or RO cases - Japan**

| OCTA grading variables | RV and/or RO<br>N=4<br>n (%) |
|---|---|
| Foveal avascular zone perimeter irregularity | 2 (50.0) |
| Superficial capillary plexus ischemia | 3 (75.0) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification
Source: Appendix 1-Table 3-4

#### 10.5.2.1.5 Common imaging features observed on ICGA - Japan

Among RV and/or RO cases, abnormalities were seen on ICGA in 7 cases (Table 10-31). Among these, the most common feature was Choroidal Hypocyanescent areas (6 cases) (Table 10-38).

**Table 10-38 Imaging features observed on ICGA with abnormalities in RV and/or RO cases - Japan**

| ICGA grading variables | RV and/or RO N=7 n (%) |
|---|---|
| Choroidal Hypocyanescent areas | 6 (85.7) |
| Early choroidal vessel hypercyanescence | 1 (14.3) |

% for "Grading variable" = number of images with grading variable/total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-4

### 10.5.2.2 Common imaging features by event type – Japan

The grading variables per imaging modality by reading center eye case classification for gradable images case cohort is discussed in this section and is presented in Table 10-39. The percentages presented below take the number of cases with the referred modality as abnormal as reference.

**Table 10-39 Grading variables per imaging modality by reading center eye case classification - Gradable images case cohort - Japan**

| Imaging modality/ Grading variables | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) |
|---|---|---|---|---|---|
| **Fluorescein Angiography (FA)** | **0** | **11 (23.9)** | **1 (50.0)** | **11 (61.1)** | **23 (34.8)** |
| Optic Nerve Head Hyperfluorescence | 0 | 6 (54.5) | 0 | 4 (36.4) | 10 (43.5) |
| Vascular Leakage | 0 | 11 (100) | 0 | 9 (81.8) | 20 (87.0) |
| Retinal ischemia | 0 | 0 | 1 (100) | 6 (54.5) | 7 (30.4) |
| Retinal Arterial Occlusion | 0 | 0 | 1 (100) | 9 (81.8) | 10 (43.5) |
| Retinal vein occlusion | 0 | 0 | 0 | 2 (18.2) | 2 (8.7) |
| Retinal vessel boxcarring | 0 | 0 | 0 | 2 (18.2) | 2 (8.7) |
| **Fundus Photography (FP)** | **17 (73.9)** | **44 (95.7)** | **2 (100)** | **17 (94.4)** | **63 (95.5)** |
| Perivascular Sheathing | 0 | 42 (95.5) | 0 | 16 (94.1) | 58 (92.1) |
| Media Opacities | 17 (100) | 18 (40.9) | 2 (100) | 10 (58.8) | 30 (47.6) |
| Retinal Hemorrhages | 0 | 13 (29.5) | 0 | 5 (29.4) | 18 (28.6) |
| Cotton-Wool Spots | 0 | 7 (15.9) | 0 | 6 (35.3) | 13 (20.6) |
| Kyrieleis Plaques | 0 | 7 (15.9) | 0 | 7 (41.2) | 14 (22.2) |
| Retinal Whitening | 0 | 7 (15.9) | 0 | 7 (41.2) | 14 (22.2) |
| Optic Nerve Swelling | 0 | 1 (2.3) | 0 | 0 | 1 (1.6) |
| Vitreous Hemorrhage | 0 | 1 (2.3) | 0 | 0 | 1 (1.6) |
| **Optical Coherence Tomography (OCT)** | **15 (65.2)** | **13 (28.3)** | **0** | **9 (50.0)** | **22 (33.3)** |

| Imaging modality/ Grading variables | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) |
|---|---|---|---|---|---|
| Hyperreflective Dots In Vitreous | 15 (100) | 12 (92.3) | 0 | 8 (88.9) | 20 (90.9) |
| Paracentral Acute Middle Maculopathy | 0 | 1 (7.7) | 0 | 1 (11.1) | 2 (9.1) |
| Inner Retinal Layer Hyperreflectivity | 0 | 0 | 0 | 4 (44.4) | 4 (18.2) |
| Retinal Nerve Fiber Layer Edema Around optic nerve | 0 | 0 | 0 | 3 (33.3) | 3 (13.6) |
| **Optical Coherence Tomography Angiography (OCTA)** | **0** | **2 (4.3)** | **0** | **2 (11.1)** | **4 (6.1)** |
| Foveal Avascular Zone Perimeter Irregularity | 0 | 1 (50.0) | 0 | 1 (50.0) | 2 (50.0) |
| Superficial Capillary Plexus Ischemia | 0 | 1 (50.0) | 0 | 2 (100) | 3 (75.0) |
| **Indocyanine Green Angiography (ICGA)** | **0** | **2 (4.3)** | **1 (50.0)** | **4 (22.2)** | **7 (10.6)** |
| Choroidal Hypocyanescent Areas | 0 | 2 (100) | 1 (100) | 3 (75.0) | 6 (85.7) |
| Early Choroidal Vessel Hypercyanescence | 0 | 0 | 0 | 1 (25.0) | 1 (14.3) |

% for modality = number of eye cases with this modality / total number of eye case per independent classification

% for “Grading variable” = number of images with Grading variable / total number of images with this imaging modality abnormal per independent classification

Source: Appendix 1-Table 3-4

#### 10.5.2.2.1 RV only imaging features - Japan

The most common features observed in patients with an abnormality on FP (n=44, 95.7%) were perivascular sheathing in 42 cases (95.5%) and media opacities in 18 cases (40.9%).

For those with an abnormality on FA (n=11, 23.9%), vascular leakage was seen in all 11 cases, optic nerve head hyperfluorescence was observed in 6 cases (54.5%).

For those with an abnormality on OCT (n=13, 28.3%), hyperreflective dots in vitreous were observed in 12 cases (92.3%) and paracentral acute middle maculopathy in 1 case (7.7%).

For those with an abnormality on OCTA (n=2, 4.3%), foveal avascular zone perimeter irregularity and superficial capillary plexus ischemia were observed in 1 case each.

For those with an abnormality on ICGA (n=2, 4.3%) choroidal hypocyanescent area was observed in both cases.

#### 10.5.2.2.2 RO only imaging features - Japan

Two cases were classified as RO only; both these cases had media opacities on FP. On FA, both retinal arterial occlusion and retinal ischemia were observed in 1 single case. One case had choroidal hypocyanescent area on ICGA.

#### 10.5.2.2.3 RV+RO only imaging features - Japan

The most common features of RV+RO seen on FA (n=11, 61.1%) were retinal arterial occlusion in 9 cases (81.8%), vascular leakage in 9 cases (81.8%), and retinal ischemia in 6 cases (54.5%). On FP (n=17, 94.4%), the most common features were perivascular sheathing in 16 cases (94.1%), media opacities in 10 cases (58.8%), and Kyrieleis plaques and retinal whitening in 7 cases each (41.2%).

On OCT (n=9 cases, 50.0%), hyperreflective dots in vitreous was observed in 8 cases (88.9%), inner retinal layer hyperreflectivity in 4 cases (44.4%), retinal nerve fiber layer edema around optic nerve in 3 cases (33.3%) and paracentral acute middle maculopathy in 1 case (11.1%).

On ICGA (n=4 cases, 22.2%), choroidal hypocyanescent area was observed in 3 cases, and early choroidal vessel hypercyanescence in 1 case. On OCTA (n=2, 11.1%), foveal avascular zone perimeter irregularity (1 case) and superficial capillary plexus ischemia (2 cases) were observed.

#### 10.5.2.2.4 IOI imaging features - Japan

The only imaging features observed in IOI eye case were hyperreflective dots in vitreous on OCT (15 cases), and media opacities on FP (17 cases).

### 10.5.2.3 Macular involvement - Japan

#### 10.5.2.3.1 Anatomical location in relation to macula - Japan

In order to characterize the anatomical locations in relation to the macula a further classification is considered, in which the cases are classified in mutually exclusive regions (involving macula, mid-periphery or periphery and any combination of their regions) as presented in Table 10-40.

In the RV and/or RO cases, the largest proportion of cases (22 cases, 33.3%) involved the macula and mid-peripheral regions, followed by the macula only (19 cases, 28.8%) and all 3 regions in 14 cases (21.2%).

No macular involvement was reported in 15.2% of cases (10 cases). Note however that wide-field imaging is required in order to detect these cases not involving the macula; which was not necessarily available for all cases.

**Table 10-40 Anatomical location in relation to the macula (alone vs. combined) by reading center eye case classification – Gradable image case cohort – Japan**

| Anatomical location in relation to macula/Location detail | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) | None N=16 n (%) |
|---|---|---|---|---|---|---|
| Macula only | 15 (65.2) | 13 (28.3) | 1 (50.0) | 5 (27.8) | 19 (28.8) | 0 |
| Macula + Mid-Periphery | 0 | 14 (30.4) | 1 (50.0) | 7 (38.9) | 22 (33.3) | 0 |
| Macula + Mid-Periphery + Periphery | 0 | 9 (19.6) | 0 | 5 (27.8) | 14 (21.2) | 0 |
| Mid-Periphery only | 0 | 4 (8.7) | 0 | 0 | 4 (6.1) | 0 |
| Mid-Periphery + Periphery | 0 | 5 (10.9) | 0 | 1 (5.6) | 6 (9.1) | 0 |

Source: Appendix 1-Table 4-4

### 10.5.2.3.2 Most common features seen in macula - Japan

As per Appendix 1-Table 4-2 (post text table), the macula was affected in the largest proportion of cases regardless of classification, followed by mid-periphery and periphery.

Among RV and/or RO cases, 55 cases (83.3%) were reported with macular involvement. Among these (n=55), the most common features observed were perivascular sheathing with 35 cases (63.6%), followed by hyperreflective dots in vitreous with 20 cases (36.4%), vascular leakage with 14 cases (25.5%). Cotton wool spots and retinal whitening was observed in 13 cases (23.6%) each. Kyrieleis plaques and retinal hemorrhages were seen in 10 cases (18.2%) each.

### 10.5.2.3.3 Imaging features seen for cases without macular involvement - Japan

Features that were seen only in the mid-periphery and periphery are included in Table 10-41. These include perivascular sheathing and retinal whitening on FP, and vascular leakage, retinal ischemia, and retinal hemorrhages on FA.

**Table 10-41 Imaging features seen without macular involvement Gradable image case cohort - Japan**

| Anatomical location in relation to macula/ Location detail | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) |
|---|---|---|---|---|---|
| **Mid-periphery only** | **0** | **4 (8.7)** | **0** | **0** | **4 (6.1)** |
| Perivascular sheathing | 0 | 4 (100.0) | 0 | 0 | 4 (100.0) |
| Retinal whitening | 0 | 1 (25.0) | 0 | 0 | 1 (25.0) |
| **Mid-periphery + Periphery** | **0** | **5 (10.9)** | **0** | **1 (5.6)** | **6 (9.1)** |
| Choroidal hypocyanescent areas | 0 | 1 (20.0) | 0 | 1 (100.0) | 2 (33.3) |

| Anatomical location in relation to macula/ Location detail | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) |
|---|---|---|---|---|---|
| Perivascular sheathing | 0 | 5 (100.0) | 0 | 1 (100.0) | 6 (100.0) |
| Retinal hemorrhages | 0 | 1 (20.0) | 0 | 1 (100.0) | 2 (33.3) |
| Retinal ischemia | 0 | 0 | 0 | 1 (100.0) | 1 (16.7) |
| Vascular leakage | 0 | 3 (60.0) | 0 | 1 (100.0) | 4 (66.7) |

% for anatomical location in relation to macula = number of eye cases with location / total number of eye case per independent classification

% for location detail= number of eye cases with location details / number of eye cases with location per independent classification

Source: Appendix 1-Table 4-6

### 10.5.2.4 Distribution of imaging features by location, extent and presence - Japan

The eye cases distribution per anatomical location are presented in Table 10-42. In RV only eye cases, retina was affected in 45 of 46 cases (97.8%). Vascular involvement was observed in 44 cases (95.7%); arteries were more involved with 41 cases (89.1%).

In RV and/or RO cases (n=66), retina was affected in 64 cases (97.0%) with vascular involvement observed in 63 cases (95.5%). Arterial involvement was seen in 56 cases (84.8%); Ischemia in 15 cases (22.7%), and vascular leakage in 20 cases (30.3%).

**Table 10-42 Anatomical location and sub-location by reading center classification - Japan**

| Anatomical location/sub-location | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) |
|---|---|---|---|---|---|
| Retina | 0 | 45 (97.8) | 1 (50.0) | 18 (100) | 64 (97.0) |
| Vascular | 0 | 44 (95.7) | 1 (50.0) | 18 (100) | 63 (95.5) |
| Arterial | 0 | 39 (84.8) | 1 (50.0) | 16 (88.9) | 56 (84.8) |
| Vein | 0 | 1 (2.2) | 0 | 1 (5.6) | 2 (3.0) |
| Both arterial and vein | 0 | 2 (4.3) | 0 | 1 (5.6) | 3 (4.5) |
| Ischemia | 0 | 2 (4.3) | 1 (50.0) | 12 (66.7) | 15 (22.7) |
| Vascular leakage | 0 | 11 (23.9) | 0 | 9 (50.0) | 20 (30.3) |
| General retina | 0 | 24 (52.2) | 0 | 12 (66.7) | 36 (54.5) |
| Vitreous | 23 (100) | 23 (50.0) | 2 (100.0) | 13 (72.2) | 38 (57.6) |
| Choroid | 0 | 2 (4.3) | 1 (50.0) | 4 (22.2) | 7 (10.6) |
| Optic nerve | 0 | 7 (15.2) | 0 | 7 (38.9) | 14 (21.2) |

The percentages are based on 'N'.

Source: Appendix 1-Table 3-2

#### 10.5.2.4.1 Occlusion types

A summary of occlusion type is presented in Table 10-43. In RV+RO only (n=18), the most common location of occlusion was branch (7 cases, 38.9%), followed by peripheral (4 cases, 22.2%).

**Table 10-43 Occlusion type by reading center eye case classification – Gradable case cohort Japan**

| Occlusion type/ Location detail | RO only N=2 n (%) | RV+RO only N=18 n (%) |
|---|---|---|
| Branch | 1 (50.0) | 7 (38.9) |
| Retinal Arterial Occlusion | 1 (100.0) | 7 (100) |
| Peripheral | 0 | 4 (22.2) |
| Retinal Arterial Occlusion | 0 | 2 (50.0) |
| Retinal Vein Occlusion | 0 | 2 (50.0) |

Source: Appendix 1-Table 5-2

### Retinal arterial and vein occlusion - Japan

Extent and location of retinal arterial and vein occlusion are presented in Table 10-44, for cases with arterial and vein involvement. For RV + RO cases, the retinal occlusion was mainly arterial, with more branch than peripheral (7 cases vs. 2 cases). For the 59 RV and/or RO cases 10 cases (17%) had arterial occlusion, however there were 2 cases that also had venous occlusion. Multiple occlusions were noted in 7 of the 10 cases of RV and/or RO in whom an arterial occlusion was detected. Arterial occlusion was observed in 10 (17%) of 59 RV and/or RO cases involving artery while vein occlusion in only 2 (40%) of 5 RV and/or RO cases involving vein. Multiple vessels were more like involved than single.

**Table 10-44 Retinal arterial and vein occlusion- Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Arterial** | **N=41** | **N=1** | **N=17** | **N=59** |
| **Retinal Arterial Occlusion n (%)** | 0 | 1 (100) | 9 (53) | 10 (17) |
| Type | | | | |
| Branch | 0 | 1 | 7 | 8 |
| Peripheral | 0 | 0 | 2 | 2 |
| Number | | | | |
| Single | 0 | 1 | 2 | 3 |
| Multiple | 0 | 0 | 7 | 7 |
| **Vein** | **N=3** | **N=0** | **N=2** | **N=5** |
| **Retinal Vein Occlusion n (%)** | 0 | 0 | 2 (100) | 2 (40) |
| Type | | | | |
| Peripheral | 0 | 0 | 2 | 2 |
| Number | | | | |

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Arterial** | **N=41** | **N=1** | **N=17** | **N=59** |
| Single | 0 | 0 | 1 | 1 |
| Multiple | 0 | 0 | 1 | 1 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

#### 10.5.2.4.2 Other imaging findings - Japan

### Perivascular sheathing - Japan

Among patients with RV and/or RO with perivascular sheathing, majority had only arterial involvement (53 cases), 1 case had only venous involvement, and 3 cases had both as shown in Table 10-45. Sheathing was observed in all three areas (macula, mid-periphery and periphery).

**Table 10-45 Extent of involvement - perivascular sheathing (Japan)**

| Location | RV and/or RO |
|---|---|
| **Arterial** | **N=59** |
| Perivascular sheathing n (%) | 56 (95) |
| Vessel type | |
| Artery | 53 |
| Both | 3 |
| Location | |
| Macula | 35 |
| Mid-periphery | 39 |
| Periphery | 16 |
| Extent | |
| Sectoral | 32 |
| Diffuse | 23 |
| **Vein** | **N=5** |
| Perivascular sheathing n (%) | 4 (80.0%) |
| Vessel type | |
| Vein | 1 |
| Both | 3 |
| Location | |
| Macula | 2 |
| Mid-periphery | 3 |
| Periphery | 3 |
| Extent | |
| Sectoral | 2 |
| Diffuse | 2 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

### Retinal Vessel Boxcarring and Kyrieleis plaque

As per Table 10-46, among RV and RO cases with arterial involvement (n=17) retinal vessel boxcarring was observed in 2 cases (12% of n=17) and in 2 cases in RV and/or RO (3.4% of n=59); there was macular involvement in all cases for both groups. Kyrieleis plaques were observed in 7 cases (41% of n=17) in RV and RO and 14 cases (24% of n=59) in RV and/or RO. Kyrieleis plaques involved the macula in the majority of cases.

**Table 10-46 Extent of involvement- Boxcarring and Kyrieleis plaque - Japan**

| Location | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Arterial** | **N=41** | **N=1** | **N=17** | **N=59** |
| Retinal vessel boxcarring n (%) | 0 | 0 | 2 (12) | 2 (3.4) |
| Location | | | | |
| Macula | 0 | 0 | 2 | 2 |
| Kyrieleis plaques n (%) | 7 (17) | 0 | 7 (41) | 14 (24) |
| Location | | | | |
| Macula | 6 | 0 | 4 | 10 |
| Mid-periphery | 3 | 0 | 3 | 6 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

### Ischemia

Table 10-47 focuses on cases with ischemia. Signs of retinal ischemia on FA were seen in 7 cases with RV and/or RO. Ischemia was seen in all three regions i.e. macula, mid-periphery, and periphery. There were no cases with retinal neovascularization. On OCT, inner retinal layer hyper-reflectivity was seen in 4 cases and paracentral acute middle maculopathy (PAMM) was observed in 2 cases with RV and/or RO. On OCT-A, 3 cases had superficial capillary plexus ischemia and 2 had FAZ perimeter irregularity.

**Table 10-47 Extent of involvement – Ischemia - Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Ischemia** | **N=2** | **N=1** | **N=12** | **N=15** |
| **Retinal ischemia n (%)** | 0 | 1 (100) | 6 (50) | 7 (47) |
| **Location** | | | | |
| Macula | 0 | 0 | 2 | 2 |
| Mid-periphery | 0 | 1 | 3 | 4 |
| Periphery | 0 | 0 | 4 | 4 |
| **Mid-periphery/periphery: extent** | | | | |
| Sectoral | 0 | 1 | 4 | 5 |
| Diffuse | 0 | 0 | 1 | 1 |
| Superficial capillary plexus ischemia n (%) | 1 (50) | 0 | 2 (17) | 3 (20) |

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| Inner retinal layer hyperreflectivity n (%) | 0 | 0 | 4 (33) | 4 (27) |
| Paracentral acute middle maculopathy n (%) | 1 (50) | 0 | 1 (8.3) | 2 (13) |
| Foveal avascular zone perimeter irregularity n (%) | 1 (50) | 0 | 1 (8.3) | 2 (13) |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

## Vascular leakage - Japan

As per Table 10-48, among 20 RV and/or RO cases in which vascular leakage was observed, the location was mainly macula (14 cases) and mid-peripheral regions (16 cases); the extent was sectoral in 9 cases and diffuse in 7 cases.

**Table 10-48 Extent of involvement - Vascular leakage - Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Vascular leakage** | **N=11** | **N=0** | **N=9** | **N=20** |
| Location | | | | |
| Macula | 7 | 0 | 7 | 14 |
| Mid-periphery | 9 | 0 | 7 | 16 |
| Periphery | 3 | 0 | 3 | 6 |
| Extent: Mid-periphery/periphery | | | | |
| Sectoral | 4 | 0 | 5 | 9 |
| Diffuse | 5 | 0 | 2 | 7 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

## Retinal whitening - Japan

As per Table 10-49, retinal whitening was mainly observed in the macula for RV and/or RO cases (13 of 14 cases); more sectoral (13 cases) than diffuse (1 case). There was no retinal whitening seen in the periphery.

**Table 10-49 Extent of involvement - Retinal whitening - Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **General retina** | **N=24** | **N=0** | **N=12** | **N=36** |
| Retinal whitening n (%) | 7 (29) | 0 | 7 (58) | 14 (39) |
| Location | | | | |
| Macula | 6 | 0 | 7 | 13 |
| Mid-periphery | 2 | 0 | 0 | 2 |
| Mid-periphery/periphery: extent | | | | |

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| Sectoral | 7 | 0 | 6 | 13 |
| Diffuse | 0 | 0 | 1 | 1 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

## Retinal hemorrhages - Japan

As per Table 10-50, retinal hemorrhages were observed in 18 cases with RV and/or RO. They were observed in the macula in 10 cases and mid periphery in 8 cases; and were sectoral in 8 cases. Majority of the cases had small hemorrhages (17 cases) and one case had mixed small and large hemorrhages. There were no cases with large hemorrhages only. Majority of retinal hemorrhages were scattered (15 cases) compared to perivenular (3 cases). Most common type of hemorrhages were dot-blot (9 cases) and pre-retinal (8 cases).

**Table 10-50 Extent of involvement - Retinal hemorrhages - Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **General retina** | **N=24** | **N=0** | **N=12** | **N=36** |
| Retinal hemorrhages n (%) | 13 (54) | 0 | 5 (42) | 18 (50) |
| Location | | | | |
| Macula | 6 | 0 | 4 | 10 |
| Mid-periphery | 6 | 0 | 2 | 8 |
| Periphery | 5 | 0 | 1 | 6 |
| Extent: Mid-periphery/periphery | | | | |
| Sectoral | 7 | 0 | 1 | 8 |
| Diffuse | 2 | 0 | 1 | 3 |
| Size | | | | |
| Small | 12 | 0 | 5 | 17 |
| Mixed | 1 | 0 | 0 | 1 |
| Pattern | | | | |
| Scattered | 11 | 0 | 4 | 15 |
| Perivenular | 2 | 0 | 1 | 3 |
| Type | | | | |
| Pre-retinal | 5 | 0 | 3 | 8 |
| Dot-blot | 7 | 0 | 2 | 9 |
| Sub-retinal | 1 | 0 | 0 | 1 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

## Cotton wool spots and cystoid macula edema - Japan

As per Table 10-51, no eye cases of cystoid macular edema were observed. Among the 13 eye cases of RV and/or RO in which cotton wool spots were observed, the location was mainly in the macula in 13 cases, extent was sectoral (11 cases), and all had a scattered pattern (13 cases).

**Table 10-51 Extent of involvement - Cotton wool spots and cystoid macula edema - Japan**

| General retina | RV only N=24 | RV+RO only N=12 | RV and/or RO N=36 |
|---|---|---|---|
| **Cotton wool spots n(%)** | **7 (29)** | **6 (50)** | **13 (36)** |
| Location | | | |
| Macula | 7 | 6 | 13 |
| Mid-periphery | 0 | 1 | 1 |
| Extent | | | |
| Sectoral | 6 | 5 | 11 |
| Diffuse | 1 | 1 | 2 |
| Pattern | | | |
| Scattered | 7 | 6 | 13 |
| **Cystoid macula edema n(%)** | **0** | **0** | **0** |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

## Vitreous involvement - Japan

As per Table 10-52, of the 38 RV and/or RO eye cases with vitreous involvement, 30 cases (79%) had media opacities on FP, and 20 cases had hyperreflective dots (53%) on OCT. Only 1 case of vitreous hemorrhage was observed (2.6%).

**Table 10-52 Extent of involvement – Vitreous - Japan**

| Vitreous | RV only N=23 | RO only N=2 | RV+RO only N=13 | RV and/or RO N=38 |
|---|---|---|---|---|
| Media opacities n (%) | 18 (78) | 2 (100) | 10 (77) | 30 (79) |
| Vitreous hemorrhage n (%) | 1 (4.3) | 0 | 0 | 1 (2.6) |
| Hyperreflective dots in vitreous n (%) | 12 (52) | 0 | 8 (62) | 20 (53) |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

## Choroid involvement

Among the 7 RV and/or RO eye cases with choroid involvement, choroidal hypocyanescent areas were observed in 6 cases, and early choroidal vessel hypercyanescence in 1 case. The pattern was mainly with discrete spots (5 cases) (Table 10-53).

**Table 10-53 Extent of involvement- Choroid - Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Choroid** | **N=2** | **N=1** | **N=4** | **N=7** |
| **Early choroidal vessel hypercyanescence n (%)** | **0** | **0** | **1 (25)** | **1 (14)** |

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Choroid** | **N=2** | **N=1** | **N=4** | **N=7** |
| **Choroidal hypocyanescent areas n (%)** | **2 (100)** | **1 (100)** | **3 (75)** | **6 (86)** |
| **Pattern** | | | | |
| Discrete spots | 2 | 1 | 2 | 5 |
| Geographic | 0 | 0 | 1 | 1 |
| **Time frame** | | | | |
| Late | 1 | 0 | 1 | 2 |
| Mid | 0 | 1 | 1 | 2 |
| **Location** | | | | |
| Macula | 0 | 1 | 2 | 3 |
| Mid-periphery | 2 | 0 | 2 | 4 |
| Periphery | 1 | 0 | 0 | 1 |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

### Optic nerve involvement - Japan

Among the 14 RV and/or RO eye cases with optic nerve involvement, 10 cases (71%) had optical nerve head hyperfluorescence on FA, 3 cases had retinal nerve fiber layer edema around optic nerve on OCT, and optic nerve swelling was seen in 1 case on FP (Table 10-54).

**Table 10-54 Optic nerve involvement - Japan**

| | RV only | RO only | RV+RO only | RV and/or RO |
|---|---|---|---|---|
| **Optic nerve** | **N=7** | **N=0** | **N=7** | **N=14** |
| Optic nerve head hyperfluorescence n (%) | 6 (86) | 0 | 4 (57) | 10 (71) |
| Time frame | | | | |
| Early | 0 | 0 | 1 | 1 |
| Late | 3 | 0 | 0 | 3 |
| Type | | | | |
| Leak | 2 | 0 | 0 | 2 |
| Stain | 0 | 0 | 1 | 1 |
| Optic nerve swelling n(%) | 1 (14) | 0 | 0 | 1 (7.1) |
| Retinal nerve fiber layer edema around optic nerve n (%) | 0 | 0 | 3 (43) | 3 (21) |

The column totals may not add up as not all characteristics were gradable or available
Source: Appendix 1-Table 6-2

### 10.5.2.5 Exploratory objective : Patient demographics- Japan

Demographic information is presented at patient level rather than eye cases level under the worse eye case classification for patient with bilateral events in Table 10-55.

Events were mainly seen in patients 70 years of age or older. Cases were reported mostly in males (68%, compared to 30% females); gender was missing for 2 cases (2%).

**Table 10-55 Patient characteristics – Gradable images case cohort – Japan**

| | IOI N=23 n (%) | RV only N=46 n (%) | RO only N=2 n (%) | RV+RO only N=18 n (%) | RV and/or RO N=66 n (%) | None N=14 n (%) |
|---|---|---|---|---|---|---|
| Age - n (%) | | | | | | |
| 50 - < 60 years | 1 (4) | 1 (2) | 0 (0) | 2 (11) | 3 (5) | 0 (0) |
| 60 - < 70 years | 3 (13) | 10 (22) | 0 (0) | 1 (6) | 11 (17) | 4 (29) |
| 70 - < 80 years | 11 (48) | 19 (41) | 1 (50) | 8 (44) | 28 (42) | 7 (50) |
| ≥ 80 years | 8 (35) | 15 (33) | 1 (50) | 7 (39) | 23 (35) | 2 (14) |
| Missing | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 1 (7) |
| Gender - n (%) | | | | | | |
| Female | 11 (48) | 12 (26) | 0 (0) | 5 (28) | 17 (26) | 3 (21) |
| Male | 12 (52) | 33 (72) | 2 (100) | 13 (72) | 48 (73) | 10 (71) |
| Missing | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (2) | 1 (7) |

Displaying case counts (i.e. patients) rather than eye case.
Cases involving bilateral events are counted under the worse eye classification considering the following hierarchy: None<IOI<RV only<RO only<RV+RO only.
Source: Appendix 1-Table 7-2

## 10.6 Adverse events/adverse reactions

Not applicable.

## 10.7 Summary of results

- Following the solicitation of image sharing for RV/RO cases reported to the Novartis safety database, a total of 231 treated and affected eyes cases with available images were identified until 31-Jan-2021 leading to 475 gradable images and 222 assessable eye cases.
- The most common images provided were FPs (175) followed by OCTs (167) and FAs (107).
- For cases classified by the reading center as RV and/or RO (144 cases) and posterior segment IOI (31 cases), the majority of gradable images received were FPs (90.3% and 87.1% respectively) followed by OCTs (65.3% and 80.6%, respectively). For the cases classified as "None", the majority of images received were OCTs (93.6%).
- Of the 222 assessable eye cases, the reading center assessed the majority of cases as RV only (72 cases), followed by RV + RO only (63 cases), None (47 cases), IOI (involving the posterior segment) (31 cases) and RO only (9 cases). This led to a total of 144 RV and/or RO eye cases.

- Nine cases were classified as RO only without RV; 3 of these had media opacities on FP. In the remaining 6, concomitant signs of inflammation could not be ruled out either due to inability to grade those parameters or lack of availability of images.
- The most common imaging features for each eye case classification were:
  1. RV only: perivascular sheathing (FP) and vascular leakage (FA)
  2. RO only: inner retinal layer hyperreflectivity on OCT; retinal artery occlusion and Retinal Ischemia (FA); retinal whitening on FP.
  3. RV+RO only: retinal arterial occlusion, vascular leakage, retinal ischemia, optic nerve head hyperfluorescence on FA and perivascular sheathing, media opacities on FP
  4. IOI involving posterior segment: hyper-reflective dots in vitreous (OCT) and media opacities (FP).
  5. RV and/or RO eye cases: Vascular leakage with FA, perivascular sheathing with FP, and vitreous hyperreflective dots with OCT.
- The majority of the cases had macular involvement. Overall, 13.9% of eyes had findings sparing the macula. Important to note however that wide-field imaging is required in order to detect mid-peripheral and peripheral involvement and this was not available for all cases.
- Most cases of occlusion were arterial. Among the patients with retinal artery occlusion, the occlusion there were more branch than central; peripheral vessels were involved in about 1/4th of cases and multiple vessels more likely than single
- Perivascular sheathing was also more common in arteries than in veins and mainly in the macula and mid-periphery locations
- Retinal Vessel Boxcarring and Kyrieleis plaques seen in about 20% and 17% of RV + RO patients, respectively and were seen more often in the macula
- Cotton wool spots were more commonly seen in macula. More often sectoral
- There were no cases of cystoid macular edema
- Most of the cases of RV and/or RO were reported from Japan (50%) and the United States (41%).
- The distribution of events was different in Japan with more cases classified as RV only (46 cases, 44%), followed by posterior segment IOI (23 cases, 22%) as compared with more RV+RO in the rest of the world. On fundus photographs, Kyrieleis plaques and perivascular sheathing and on OCT, hyper-reflective dots in the vitreous were seen more often in patients from Japan compared to the rest of the world.
- Most of the events occurred in patients over 70 years of age and in females. However, the gender ratio was reversed in the Japanese cases (number of males greater than females) when compared to the general population.

# 11 Discussion

## 11.1 Key results

- A total of 475 gradable images were received from 222 eye cases in 198 patients. The most common images provided were **fundus photographs** followed by **OCTs** and then

**fluorescein angiograms**. This was the largest descriptive analysis of imaging features associated with brolucizumab-related inflammation., taken at the time of event occurence.

- The majority of cases were classified as RV only (n=72 cases), followed by RV+RO only (n=63 cases), and then posterior segment IOI (n=31 cases). Additional n=9 cases were classified as RO only and n=47 cases as "None".
- The most common imaging variable seen in cases with RV and/or RO patients with an abnormality seen on: **FA** was vascular leakage (90% of cases); on **FP** was perivascular sheathing (83% of cases), and on **OCT** was hyperreflective dots in the vitreous (64% of cases).
- Majority of the cases had macular involvement. At least 13.9% of eyes had findings sparing the macula.
- Retinal occlusion was mainly arterial; more branch than central; peripheral vessels were involved in about 1/4th of cases and multiple vessels more likely than single.

## 11.2 Limitations

The bias under the study has been covered in Section 9.6.

- Limitations inherent to post-marketing reporting systems included under-reporting, incompletely documented cases, lack of standardization of imaging and cases without adequate imaging information. As post-marketing adverse event reporting is voluntary, this may lead to potential selective reporting and results may not be representative for all cases.
- The majority of AEs reported to Novartis in the post-marketing setting was IOI. However images were requested only from cases with RV/RO. Even amongst this population, images were not provided for all cases; and when provided not all images modalities were provided. The case classification is therefore intrinsically linked to and limited by the provided images.
- In addition, as per standard pharmacovigilance practice, the information is reported at case level in the Novartis safety database rather than eye case level leading to information not necessary been captured in a structured manner or retrievable in a systematic manner to allow programmatical exploitation.
- 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.
- Due to the real world nature of the study, all images provided by physician were accepted, i.e. no standardization of images or image acquisition could be imposed. As a consequence, for some cases mid-peripheral and peripheral images were not available and not all imaging modalities were available.
- Only signs of posterior segment inflammation were evaluated.
- Some of the observed imaging parameters may not necessarily be associated with clinical symptoms and may lack clinical significance.

- No control images were available i.e. the images provided only included cases involving RV/RO or IOI per initial reporter judgement and not allowed to perform a concordance analysis.
- There was no classification of RO with IOI. This is important as among cases of RO without RV, 3 cases had media opacities on FP. In the remaining 6 cases, concomitant signs of inflammation could not be ruled out either due to inability to grade those parameters or lack of availability of images.

## 11.3 Interpretation

The purpose of this study was to describe the most common imaging features associated with inflammation in patients treated with brolucizumab in the post-marketing setting. These are well-known features of inflammation. As a result, there were unique inherent limitations as compared to a clinical trial data set. The imaging modalities and image acquisition were not standardized across all the cases. In addition, not all cases had a complete data set of the images. In particularly not all cases had wide field imaging which would have been necessary to detect involvement outside of the macula ie in mid -periphery and periphery. There was variability in the quality of images obtained. Additionally, the images were evaluated in the setting of an inflammatory AE which itself impacts the ability to obtain good quality images. Also, the differences in classification between Japan vs the rest of the world (mainly US) could be attributed to the timing of approval and increased awareness of the safety signal of RV and/or RO at the time of launch in Japan as compared to when it was launched in the US. Nonetheless, because RV and/or RO is an uncommon AE, it would be difficult to obtain these results in a clinical trial setting. Therefore the key strengths of this study are the standardized interpretation of these images and standardized imaging based classification.

## 11.4 Generalizability

Due to the study design applied and unique inherent limitations described above, we cannot conclusively say that the observations made in this cohort would universally apply. Therefore physicians must keep the limitations described above when interpreting the percentages ascribed. Also as not all patients had wide-field images, it is important to remember that findings may be seen outside of the posterior pole. Finally, these imaging findings do not detract from a detailed dilated ocular examination done by the physician.

# 12 Other information

Not applicable.

# 13 Conclusion

This study expanded the knowledge of the real world practice related to handling of the inflammatory events with respect to ophthalmological images obtained at the time of the inflammatory event in patients treated with brolucizumab. This is the largest descriptive analysis of imaging features in these cases and were analyzed in a standardized manner. The most common imaging variable seen in cases with RV and/or RO patients with an abnormality on FA was vascular leakage (90% cases); on FP was perivascular sheathing (83% cases), and

on OCT was hyperreflective dots in the vitreous (64%). However, there were a few patients with less-common findings such as Kyrieleis plaques etc. Additionally, while majority of the cases had macular involvement, at least 13.9% of eyes had findings sparing the macula. Accordingly, this dataset provides valuable information on the risk of posterior segment inflammatory and anatomical changes occurring in patients treated with brolucizumab and may further guide clinical practice by informing physicians on both common and uncommon features to evaluate for in order to detect and further treat the events.

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# Appendices

## Appendix 1 – List of stand-alone documents

Investigator list and Investigator signatory page

Case assessment form

Grading forms

Tables, figures and listings

## Appendix 2 – Additional relevant information (available upon request)

Protocol and protocol amendments

Documentation of statistical methods