NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**INCIDENCE OF RETINAL VASCULITIS WITH OR WITHOUT RETINAL VASCULAR OCCLUSION AMONG EYES TREATED WITH APPROVED ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OR DIABETIC MACULAR EDEMA AS RECORDED IN ELECTRONIC HEALTH RECORDS**
PROTOCOL NUMBER:	CR45271
VERSION NUMBER:	2.0
EU PAS REGISTER NUMBER:	EUPAS107730
STUDIED MEDICINAL PRODUCTS:	Faricimab
AUTHOR:	[redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
06-Dec-2023 07:56:19	Deputy EU QPPV	[redacted]

ACTIVE SUBSTANCES:	S01LA09: faricimab
PRODUCT REFERENCE NUMBERS:	RO6867461
PROCEDURE NUMBER{S}:	Not applicable
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The purpose of the study is to assess and compare the incidence of retinal vasculitis and retinal vasculitis with retinal vascular occlusion across eyes treated with different approved intravitreal anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration or diabetic macular edema using electronic health records.
COUNTRY OF STUDY POPULATION:	United States
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ASRS	American Society of Retina Specialists
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
DCC	Distance with Correction
DSC	Distance without Correction
DME	Diabetic Macular Edema
ETDRS	Early Treatment Diabetic Retinopathy Study
HCPCS	Healthcare Common Procedure Coding System
GA	Geographic Atrophy
GPP	Good Pharmacoepidemiology Practice
ICD-10	International Classification of Diseases 10 Clinical Modification
ICSR	Individual Case Safety Report
IOI	Intraocular Inflammation
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
MAH	Marketing Authorization Holder
nAMD	Neovascular Age-related Macular Degeneration
NCC	Near with Correction
NSC	Near without Correction
NI-PASS	Non-Interventional Post Authorization Safety Study
PHI	Personal Health Information
PH	Pinhole
RO	Retinal Vascular Occlusion
RV	Retinal Vasculitis
RVO	Retinal Vein Occlusion
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

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3. ABSTRACT/SYNOPSIS

TITLE:	**INCIDENCE OF RETINAL VASCULITIS WITH OR WITHOUT RETINAL VASCULAR OCCLUSION AMONG EYES TREATED WITH APPROVED ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OR DIABETIC MACULAR EDEMA AS RECORDED IN ELECTRONIC HEALTH RECORDS**
PROTOCOL NUMBER:	CR45271
VERSION NUMBER:	2.0
DATE OF SYNOPSIS:	1 December 2023
EU PAS REGISTER NUMBER:	EUPAS107730
STUDIED MEDICINAL PRODUCT:	Faricimab
SCIENTIFIC RESPONSIBLE	[redacted] MD MBA Genentech, Inc.
MAIN AUTHOR	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Neovascular age-related macular degeneration, diabetic macular edema
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

Rationale and Background

Intraocular inflammation (IOI) is a well-known risk associated with intravitreal (IVT) therapies and is considered a broad medical concept that includes retinal vasculitis (RV) with or without retinal vascular occlusion (RO). RV and RV with RO are considered more severe manifestations of IOI. Reports of RV with or without RO exist with multiple IVT treatments, but more predominantly with brolucizumab and now more recently with pegcetacoplan (American Society of Retina Specialists 2020, Monés et al. 2020, Do 2020, American Society of Retina Specialists 2023, Ma et al. 2022, Schmidt-Ott et al. 2023). However, the incidence of these events among eyes receiving approved IVT anti-

vascular endothelial growth factor (VEGF) treatments for neovascular age-related macular degeneration (nAMD) or diabetic macular edema (DME) is not well-characterized in the literature.

Research Question and Objectives

The primary objective for this study is as follows:

- Assess and compare the incidence of RV, RV with RO, and IOI (including RV) with RO events across eyes treated with different approved IVT anti-VEGF agents after diagnosis of nAMD or DME, as recorded in an electronic health record (EHR) database.

The secondary objectives for this study are as follows:

- Summarize the demographic and clinical characteristics of study eyes.
- Among eyes with events, summarize the characteristics of anti-VEGF treatments received, including but not limited to the number of injections received, type of anti-VEGF agents received, time to event, and vision change and severe vision loss following the event.

Study Design

Secondary data use/ retrospective observational cohort study

Data Sources

Vestrum Health EHR Data (data are available from 2014 to 2023)

Population

Patient eyes with nAMD or DME seen at private retina specialist clinics in the routine clinical care setting in the United States

Variables

Primary Safety Variables

The primary variables for this study are as follows:

- Number of eyes with RV, RV with RO, or IOI (including RV) with RO events
- Number of eyes at risk
- Percent of eyes with an event
- Number of events of RV, RV with RO, or IOI (including RV) with RO
- Number of injections
- Incidence of the events

Secondary Variables

The secondary variables for this study are as follows:

- Age at index (first) anti-VEGF treatment in the study
- Gender
- Region
- Treatment indication
- For eyes with an event
  - Prior types of anti-VEGF agents received
  - Number of anti-VEGF injections before the first event

    - Number of injections received of the most recent type of anti-VEGF agent prior to the event
    - Time to event onset from the first anti-VEGF injection ever received
    - Time to event onset from the most recent anti-VEGF injection prior to the event
    - Time to event onset from the first injection of the most recent type of anti-VEGF agent received prior to the event
    - Number of different agents received prior to the event
    - Visual acuity (VA) change between the most recent visit prior to the event and the event visit
    - Severe vision loss (defined as a loss of ≥30 converted Early Treatment Diabetic Retinopathy Study (ETDRS) letters (see section 8.3.2)) between the most recent visit prior to the event and the event visit)
    - Prior treatment status: 1) Switcher 2) treatment naïve
- For switcher eyes:
    - Number of eyes with ≥2 prior anti-VEGFs agents
    - Distribution of anti-VEGF agent types received immediately prior to switch
- Ocular medical history
- Concomitant ocular treatments

Study Size

The Vestrum Health database includes over 2.2 million patients at the time of protocol writing. The final sample size in the study will vary according to the study period and the eligibility criteria for the study.

Data Analysis

The incidence of RV, RV with RO, and IOI (including RV) with RO may be summarized using the number (%) of patient eyes at risk with events, the number of events per 1,000 injections (or 10,000 injections, etc., as appropriate), and the incidence rate (number of events/eye-time).

Continuous or numeric variables will be summarized descriptively using mean, median, standard deviation, quartile 1, quartile 3, minimum, and maximum. Categorical variables will be summarized using number (%).

The relative risk of RV, RV with RO, and IOI (including RV) with RO events by different anti-VEGF agents compared to a reference agent will be calculated without adjusting for covariates, or assessed using regression modeling, depending on the number of events. The risk difference may also be calculated.

Confidence intervals will be provided as appropriate.

The data to be extracted initially were collected between 2014-2023; however, the analyses may consider alternative time periods to account for potential surveillance or reporting bias due to increased awareness of these events following brolucizumab launch.

Milestones

First Data Extraction:
The first data extraction is the date from which the variables used for the analysis as per protocol start to be extracted. The planned first data extraction is 20 October 2023.

Last Data Extraction:
The last data extraction is the date from which the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) is completely available. The planned last data extraction date is 20 October 2023 – 30 June 2024.

4. AMENDMENTS AND UPDATES

see table below

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	December 2023 (see protocol signature date)	Sections 3, 7 and 8	Removed objectives and analysis details on background incidence, and diabetic retinopathy, retinal vein occlusion, and geographic atrophy. Clarified that the comparative safety analysis focuses on approved intravitreal anti-VEGF agents for nAMD and DME. Additional minor changes have been made to improve clarity and consistency. This amendment represents cumulative changes to the original protocol.	Change in study scope

5. MILESTONES

Milestone	Planned Date
Registration of protocol in the EU PAS register	December 2023
First Data Extraction	20 October 2023
Last Data Extraction	20 October 2023 – 30 June 2024
Final report of study results (CSR)	1 April 2024 – 31 March 2025
Registration of the results in the EU PAS register	1 April 2025 – 31 March 2026
Publication submission	1 April 2024 – 31 March 2025

6. RATIONALE AND BACKGROUND

Intraocular inflammation (IOI) is a well-known risk associated with intravitreal (IVT) therapies and is considered a broad medical concept that includes retinal vasculitis (RV) with or without retinal vascular occlusion (RO). RV and RV with RO are considered more severe manifestations of IOI. Reports of RV with or without RO exist with multiple IVT treatments, but more predominantly with brolucizumab and now more recently with pegcetacoplan (American Society of Retina Specialists 2020, Monés et al. 2020, Do 2020, American Society of Retina Specialists 2023, Ma et al. 2022, Schmidt-Ott et al. 2023).

Shortly after brolucizumab approval in October 2019, cases of RV with or without RO following brolucizumab treatment were reported to the American Society of Retina Specialists (ASRS) (American Society of Retina Specialists 2020). The ASRS Research and Safety in Therapeutics (ReST) Committee analyzed 26 eyes of 25 patients with reported RV cases following brolucizumab treatment and reported that the majority had occlusive disease and half had substantial decrease in vision at the final follow-up (Witkin et al. 2020). As a result of these findings, Novartis commissioned an external Safety Review Committee to independently assess post-marketing reports of patients treated with brolucizumab and to reevaluate ocular inflammatory adverse events from HAWK and HARRIER, two phase 3 randomized controlled clinical trials comparing the efficacy and safety of brolucizumab vs aflibercept 2 mg in eyes with neovascular age-related macular degeneration (nAMD) (Dugel et al. 2019, Dugel et al. 2020). The Safety Review Committee reported that in HAWK and HARRIER, IOI of any form was identified in 4.6% (50 of 1,088) of study eyes treated with brolucizumab (Monés et al. 2020). Concomitant RV was present in 36 of the 50 eyes with IOI (3.3% of total study eyes), and of those, 23 eyes had concomitant RO (2.1% of total study eyes) (Monés et al. 2020). In post-marketing surveillance data for brolucizumab (October 2019-November 2022), there were 5.6 events per 10,000 injections for RV and 5.0 events per 10,000 injections for RV with RO (Novartis AG 2023).

In addition to brolucizumab, post-market reports of RV with or without RO have also been reported at a lower frequency for aflibercept and ranibizumab (Ma et al. 2022, Schmidt-Ott et al. 2023). A case of RV with RO following aflibercept treatment was also identified during the re-evaluation of HAWK and HARRIER as conducted by the Safety Review Committee (American Society of Retina Specialists 2020, Do 2020).

In addition to IVT anti-VEGF therapies, occurrence of RV with or without RO were also reported among eyes treated intravitreally with pegcetacoplan injections for geographic atrophy (GA). On July 15, 2023, the ASRS published reports of RV with RO among GA patients following treatment with pegcetacoplan (American Society of Retina Specialists, 2023).

While RV with or without RO have been reported among eyes receiving IVT treatments, the incidence of these events is not well-characterized in the literature. The main objective of this study is to assess and compare the incidence of RV, RV with RO, and IOI (including RV) with RO among eyes with nAMD or diabetic macular edema (DME) treated with different approved anti-VEGF IVT agents for these indications. Characteristics of eyes with and without events will also be summarized.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The purpose of the study is to understand the incidence of RV with or without RO among eyes treated with different approved IVT anti-VEGF agents for nAMD or DME.

7.2 OBJECTIVES

The primary objective for this study is as follows:

- Assess and compare the incidence of RV, RV with RO, and IOI (including RV) with RO events across eyes treated with different approved IVT anti-VEGF agents after diagnosis of nAMD or DME, as recorded in an electronic health record (EHR) database.

The secondary objectives for this study are as follows:

- Summarize the demographic and clinical characteristics of study eyes.
- Among eyes with events, summarize the characteristics of anti-VEGF treatments received, including but not limited to the number of injections received, type of anti-VEGF agents received, time to event, and vision change and severe vision loss following the event.

8. RESEARCH METHODS

8.1 STUDY DESIGN

This is a secondary data use, retrospective observational cohort study. The study will analyze anonymized EHR data from private retina specialists in the United States to

assess the incidence of RV, RV with RO, and IOI (including RV) with RO among eyes with nAMD or DME. Incidence will be assessed among eyes treated with IVT anti-VEGF agents approved in nAMD or DME. The EHR records longitudinal information on patient diagnosis, treatments, and outcomes, which allows the assessment of incident adverse events and the temporality of treatments relative to the adverse events. Moreover, this EHR database using information from retina specialists contains data on VA, which allows for the assessment of potential vision changes following the occurrence of an adverse event. This project was considered exempt from institutional review board (IRB) review as the research involves only the analysis of existing data that are anonymized.

8.2 SETTING

The study will include patient eyes from the Vestrum Health database, which includes data from EHRs from private retina specialists in the United States. The eligibility criteria are below. Patient eyes diagnosed with nAMD or DME will be identified using *International Classification of Diseases 9/10 Clinical Modification* (ICD-9/10-CM) diagnosis codes. Eyes not coming from active practices in the Vestrum database will not be included.

Although data are available from 1 January 2014 to 30 September 2023 within the Vestrum database, the analyses may consider alternative time periods to account for potential surveillance or reporting bias due to increased awareness of these events following brolucizumab launch.

8.2.1 Inclusion and exclusion criteria

Inclusion criteria

- Eyes diagnosed with nAMD or DME that received at least 1 anti-VEGF treatment between 1 January 2014 and 31 March 2023 following the date of the index diagnosis
- Patients aged ≥18 years at the index (first) anti-VEGF treatment during the study period
- Eyes with at least one visit following the index anti-VEGF treatment

Exclusion criteria

- Eyes with an incident IOI, RV, or RO on or prior to the index anti-VEGF treatment date

8.2.2 Event follow-up

For eyes treated with an IVT therapy, eyes are considered to be at risk for the adverse event of RV, RV with RO, or IOI (including RV) with RO up to 180 days after each IVT injection. Each of the 3 events (RV, RV with RO, and IOI (including RV) with RO) will be assessed separately. For example, when identifying RV events, RV diagnosis codes will be identified irrespective of whether the eye had an IOI or RO diagnosis during the follow-up. For each event follow-up, only one event per eye will be captured. For example, when assessing RV with RO, IVT treated eyes will be followed until they have an event of RV with RO (the full case definition of having both diagnoses codes must be

met), or until the end of their at-risk period or the end of the study, whichever is earlier. The at-risk period for all events is up to 180 days after each anti-VEGF injection and is defined as the time of the last injection to the earliest of the next injection, the event of interest, the eye's last visit, the study end, or 180 days after the injection.

The event onset date (of the full event of RV, RV with RO, and IOI (including RV) with RO) will be defined as the date that the full case definition is met. For example, an eye may have a diagnosis of RV on day 30 of follow-up and a diagnosis of RO on day 60 of follow-up. The event onset date for RV with RO will be day 60, when the full case definition is met. Of note, however, for this same eye, the event onset date for the RV event (regardless of RO) will be day 30. In addition, the event will be counted under the most recent anti-VEGF agent received before the full case definition is met. For example, RV alone will be counted under the most recent anti-VEGF agent received before RV onset, and RV with RO will be counted under the most recent anti-VEGF agent received before the full event of RV with RO is met. If there is a switch in agents after RV onset and before the full RV with RO case definition is met, then these two events (RV and RV with RO) would count toward different anti-VEGF agents.

8.3 VARIABLES

8.3.1 Primary Safety Variables

The occurrence of the following adverse events are of primary interest:

- RV
- RV with RO
- IOI (including RV) with RO

These events will be identified using ICD-9/10-CM diagnosis codes recorded in the EHR. RV is the only event identified using a single ICD-9-CM (362.18) code or ICD-10-CM code (H35.06X). Because there is no ICD-9/10-CM code for RV with RO, we utilized a combination of ICD-9/10-CM codes to identify eyes with RV with RO. Specifically, RV with RO events are defined as having the RV code in addition to the RO code in the table below. Similarly, IOI (including RV) with RO is defined as having the IOI code in addition to the RO code. The codes are allowed to occur on separate days. Of note, RV is included in the list of codes for IOI. The codes are adapted from a study of adverse events among brolucizumab in the American Academy of Ophthalmology Intelligent Research In Sight registry and Komodo Healthcare Map (Khanani et al. 2021). However, Khanani et al. identified cases of 1.) IOI or RO and 2.) RV or RO.

Events of RV, RV with RO, and IOI (including RV) with RO identified as described above depend on ICD-9/10-CM codes that are recorded by retina specialists in the EHR. These events are not confirmed cases and assessment of fluorescein angiography images, the gold standard method for diagnosing RV with or without RO, is not available to confirm the events identified from diagnosis codes.

Adverse Event	ICD-10-CM Code	ICD-9-CM Code

Intraocular Inflammation (IOI) – Includes RV		
Acute and Subacute Iridocyclitis	H20.0X (excluding H20.03X , H20.04X and H20.05X)	364.00 Acute and subacute ir–docyclitis - unspecified 364.01 Primary iridocyclitis 364.02 Recurrent iridocyclitis
Chronic Iridocyclitis	H20.1X	364.10 Chronic ir–docyclitis - unspecified 364.11 Chronic iridocyclitis in diseases classified elsewhere
Other Iridocyclitis	H20.9	364.3 Unspecified iridocyclitis
Posterior Synechiae	H21.54X	364.71 Posterior synechiae of iris
Focal Chorioretinal Inflammation, Juxtapapillary	H30.0X	363.00 Focal chor–oretinitis - unspecified 363.01 Focal choroiditis and chor–oretinitis - juxtapapillary 363.03 Focal choroiditis and chorioretinitis of other posterior pole 363.04 Focal choroiditis and chor–oretinitis - peripheral 363.05 Focal retinitis and retino–horoiditis - juxtapapillary 363.06 Focal retinitis and retino–horoiditis - macular or paramacular 363.07 Focal retinitis and retinochoroiditis of other posterior pole 363.08 Focal retinitis and retino–horoiditis - peripheral
Disseminated Chorioretinal Inflammation, Peripheral	H30.1X	363.10 Disseminated chorioretinitis - unspecified 363.11 Disseminated choroiditis and chorioretinitis - posterior pole 363.12 Disseminated choroiditis and chorioretinitis - peripheral 363.13 Disseminated choroiditis and chorioretinitis - generalized 363.14 Disseminated retinitis and retinochoroiditis - metastatic 363.15 Disseminated retinitis and retinochoroiditis - pigment epitheliopathy
Posterior Cyclitis (Pars Planitis)	H30.2X	363.21 Pars planitis
Other Chorioretinal inflammations	H30.8X	363.22 Harada's disease
Unspecified Chorioretinal Inflammation	H30.9X	363.20 Chorioretinitis - unspecified
Changes in Retinal Vascular Appearance (Vascular Sheathing)	H35.01X	362.13 Changes in vascular appearance of retina
Exudative Retinopathy	H35.02X	362.12 Exudative Retinopathy
Vitritis/Other disorders of Vitreous Body	H43.89	379.29 Other disorders of vitreous
Unspecified Papilledema	H47.10	377.00 Papilledema, unspecified
Papilledema associated with decreased ocular pressure	H47.12	377.02 Papilledema associated with decreased ocular pressure
Papilledema associated with retinal disorder	H47.13	377.03 Papilledema associated with retinal disorder

Optic neuritis (optic papillitis, retrobulbar neuritis, toxic optic neuropathy, other optic neuritis, unspecified optic neuritis)	H46X (excluding H46.2 for nutritional optic neuropathy)	377.30 Optic neuritis - unspecified 377.31 Optic papillitis 377.32 Retrobulbar neuritis (acute) 377.34 Toxic optic neuropathy 377.39 Other optic neuritis
Panuveitis	H44.11X	360.12 Panuveitis
Retinal Vasculitis	H35.06X	362.18 Retinal Vasculitis
Retinal Vascular Occlusion		
Retinal Artery Occlusion (RAO)	H34.0X (Transient retinal artery occlusion); H34.1X (Central retinal artery occlusion); H34.21X (Partial retinal artery occlusion); H34.23X (Retinal artery branch occlusion)	362.31 Central retinal artery occlusion 362.32 Retinal arterial branch occlusion 362.33 Partial retinal arterial occlusion 362.34 Transient retinal arterial occlusion
Retinal Vein Occlusion (RVO)	H34.81X (Central retinal vein occlusion); H34.83X (Branch retinal vein occlusion)	362.35 Central retinal vein occlusion 362.36 Venous tributary (branch) occlusion
Unspecified RO	H34.9 (Unspecified retinal vascular occlusion)	362.30 Retinal vascular occlusion - unspecified
Ischemic Optic Neuropathy	H47.01X (Ischemic optic neuropathy)	377.41 Ischemic optic neuropathy

Primary Safety Variables

The primary variables for this study are as follows:

- Number of eyes with RV, RV with RO, or IOI (including RV) with RO events
- Number of eyes at risk
- Percent of eyes with an event
- Number of events of RV, RV with RO, or IOI (including RV) with RO
- Number of injections
- Incidence of the events

8.3.2 Secondary Variables

Secondary Variables

The secondary variables for this study are as follows:

- Age at index (first) anti-VEGF treatment in the study
- Gender
- Region
- Treatment indication
- For eyes with an event
  - Prior types of anti-VEGF agents received
  - Number of anti-VEGF injections before the first event

    - Number of injections received of the most recent type of anti-VEGF agent prior to the event
    - Time to event onset from the first anti-VEGF injection ever received
    - Time to event onset from the most recent anti-VEGF injection prior to the event
    - Time to event onset from the first injection of the most recent type of anti-VEGF agent received prior to the event
    - Number of different agents received prior to the event
    - Visual acuity (VA) change between the most recent visit prior to the event and the event visit
    - Severe vision loss (defined as a loss of ≥30 converted Early Treatment Diabetic Retinopathy Study (ETDRS) letters (see section 8.3.2)) between the most recent visit prior to the event and the event visit)
    - Prior treatment status: 1) Switcher 2) treatment naïve
- For switcher eyes:
    - Number of eyes with ≥2 prior anti-VEGFs agents
    - Distribution of anti-VEGF agent types received immediately prior to switch
- Ocular medical history
- Concomitant ocular treatments

Other variables

Anti-VEGF Injections

Medications administered by the treating retina specialist are identified using the structured field containing the relevant J-Code. Dates of administration are the dates of the patient visit describing the treatment delivered. Procedure medications received along with the associated procedure record and Current Procedural Terminology (CPT) codes are used in conjunction with J-Codes to identify both the procedure performed and all associated medications used.

Treatment with anti-VEGF is identified using the following Healthcare Common Procedure Coding System (HCPCS) codes along with CPT codes.

HCPCS

- Ranibizumab (Lucentis) – J2778, C9233
- Aflibercept (Eylea) – J0178, C9291, Q2046
- Brolucizumab (Beovu) – J0179
- Faricimab (Vabysmo) – J2777
- Ranibizumab-nuna (Byooviz) – Q5124
- Ranibizumab-eqrn (Cimerli) – Q5128
- Bevacizumab (Avastin) – J9035, C9257, J7999 (IVT use is considered an off-label use of bevacizumab, and therefore is not an appropriate treatment for comparative safety analyses with approved anti-VEGF agents; therefore, bevacizumab safety will not be assessed specifically in this study; however, eyes treated with approved anti-VEGF agents might have IVT bevacizumab exposure, so bevacizumab exposure needs to be accounted for to enable appropriate analyses)

CPT

- 67028 – Intravitreal Injection

Vestrum also accepts incoming procedure medication that is associated with an unclassified drug J-Codes J3490, J3590, provided that there is a text entry outlining the drug being administered. Examples of these incoming entries are: “J3490 Eylea 3 mg”, “J3490 eylea-sample”, “J3490 Lucentis 0.5”. A Vestrum proprietary algorithm is used to assign these unclassified drug codes to the appropriate drug using the text entry.

Visual Acuity

Vestrum Health receives VA data from Snellen charts in over 98% of patient visits, with some other types (e.g., Jaeger charts) in the remainder. There are five different VA measurement types that are received and used in analysis;

1. Distance (20ft) with correction (DCC)
2. Distance without correction (DSC)
3. Near (40cm) with correction (NCC)
4. Near without correction (NSC)
5. Pinhole (PH) vision.

There are no instances of ETDRS being received since all data are coming from private retina clinics. All VA entries are standardized and converted to ETDRS letters for reporting purposes. Vestrum’s standard output for VA is in the form of **Converted ETDRS = 85 + 50*Log (Snellen)** (Gregori, et al. 2010).

The current analysis will only compare VA results of a patient if vision is taken by the same measurement method. Should a visit have multiple measurements, the ranking order for measurement types is DCC ->NCC ->PH ->DSC ->NSC.

8.4 DATA SOURCE(S)

Vestrum Health Database

Vestrum Health was founded in 2014 and its database consists of de-identified data from EHRs from a geographically diverse panel of United States-based private retina specialists. All data comes exclusively from private retina clinics; Vestrum does not collect data from hospitals or institutions. Approximately 70% are retina-only clinics and about 30% are multispecialty clinics. Vestrum contracts with practices to obtain most fields contained in the EHR. Vestrum maintains Business Associate Agreements with each practice. Practices authorize its software vendor to send all EHRs to Vestrum weekly. Longitudinal patient records are identified by an anonymized patient code assigned by the software vendor. The data are sent by file transfer protocol and loaded to the Vestrum input server. Data from multiple sources are organized into the structured database residing in United States-based cloud servers. Data are maintained in a secure, password-protected environment using standards associated with Personal Health Information (PHI).

The data collected by Vestrum is in the form of de-identified EHRs, and as such, the data do not affect or influence the treatment the patient receives. It has been generally accepted that studies based on anonymized historic electronic health record data do not require IRB review or approval. This study was considered IRB exempt based on this.

Data Representativeness

Vestrum's database is a collection of multiple different EHR systems, totaling up to >360 physicians and >65 practices across all regions in the United States. Data from some physicians begin in 2013 with complete coverage for all specialists beginning by 2015. This applies to newly enrolled practices into the Vestrum panel as all back data for the practice are provided at the time of enrollment.

Vestrum Panel Regional Distribution vs National Distribution of Retina Specialists		
Region	Proportion of Physicians	
	Vestrum Panel	National Estimate (ASRS/ Centers for Medicare & Medicaid Services (CMS))
Midwest	20%	21%
Northeast	17%	24%
Southeast	27%	24%
Southwest	11%	10%
West	26%	21%

The Vestrum panel includes data from a range of practice sizes but is skewed towards larger practices compared to the national US estimate (estimate has been taken from a combination of the ASRS list of retina specialists and the CMS reporting on anti-VEGF injecting ophthalmologists). Internal Vestrum analyses have not found evidence to suggest that patient populations or treatments delivered differ by practice size.

Vestrum Panel Practice Size Distribution vs National Distribution of Retina Specialists		
Practice Size	Proportion of Practices	
	Vestrum Panel	National Estimate (ASRS/CMS)
1	17%	44%
2-5	45%	42%
6-10	20%	10%
11+	17%	3%

8.5 STUDY SIZE

The Vestrum Health database includes over 2.2 million patients. Estimates of the number of patients and eyes in the Vestrum database as of October 2022 are available for a subset of the retinal indications of interest below. The final sample size in the study will vary according to the available data for the study period and the eligibility criteria for the study.

Retinal indication	Patients	Eyes
nAMD	255,003	363,074
DME	194,610	329,376

8.6 DATA MANAGEMENT

Vestrum Health will be responsible for the data management of this research, including quality checking of the data. Vestrum Health extracts data weekly from various EHR vendors where it is stored on secure servers accessible only to Vestrum employees. Vestrum has multiple data warehouses where an iterative standardization is applied to the data to combine different sources and ensure data accuracy.

The EHR information is loaded into the input database unchanged. The incoming data are subject to quality control steps to ensure all the expected data are received and files are complete and readable. Changes in historic data are labeled as such and both original and modified values are retained. This server constitutes a back-up system and is accessible by a very limited number of Vestrum personnel.

Input data are transformed into the operational database through a process to ensure values are within specified limits, incidental PHI contained in text fields are removed, information in text strings that contain multiple data elements are broken down into separate analyzable cells, coding is standardized, and each data set is updated. Some of the steps in the validation process compare information in text fields with CPT and J-codes to ensure accuracy. The database is comprised of approximately 2,000 cells in 300 files, all linked through a coding structure.

Once all data cleansing and standardizing has been performed by Vestrum, a static dataset is created specifically for the study to ensure there will be no variation in data for its duration. At this point, data are accessible for analysis through Microsoft Structured query language Server Management Studio 18 and the building of the patient population begins. All metrics relevant to the analysis are extracted in aggregated form to Excel for further analysis and output generation. The statistical software used for this analysis will be R – version 3.6.3, which will be used for any statistical analysis performed (t-tests, chi-square test or proportion, confidence intervals etc.). Graphs and tables will be generated using both R and Excel, where applicable.

Following the extraction from the data source, anonymized data will be stored at Vestrum's databases. Access to the data will be restricted to Vestrum personnel. No personal data will be provided to Roche/Genentech.

8.7 DATA ANALYSIS

8.7.1 Safety Analyses

The primary analyses involve identifying the occurrence of the following adverse events: RV, RV with RO, and IOI (including RV) with RO among eyes with nAMD or DME. Eyes with each retinal indication will be identified using ICD-9/10-CM codes. Among eyes with multiple indications, eyes will be assigned to the first retinal indication diagnosed.

The incidence of RV, RV with RO, IOI (including RV) with RO may be summarized using the number (%) of patient eyes at risk with events, the number of events per 1,000 injections (or 10,000 injections, etc. as appropriate), or the incidence rate (number of events/eye-time).

Continuous or numeric variables will be summarized descriptively using mean, median, standard deviation, quartile 1, quartile 3, minimum, and maximum. Categorical variables will be summarized using number (%).

The relative risk of RV, RV with RO, and IOI (including RV) with RO events by different anti-VEGF agents compared to a reference agent will be calculated without adjusting for covariates, or assessed using regression modeling, depending on the number of events. The risk difference may also be calculated. Possible approaches may include Poisson (or modified Poisson), negative binomial, or logistic regression. Regression diagnostics will be used to evaluate model assumptions. Generalized estimating equations or mixed models may be used to account for the correlation between two eyes within the same patient, and/or multiple injections within the same eye. Potential confounders such as sex or prior treatment will be evaluated for adjustment.

Confidence intervals will be provided as appropriate.

8.7.2 Other Analyses

Summary of the characteristics of the patient eyes

Continuous or numeric variables will be summarized descriptively using mean, median, standard deviation, quartile 1, quartile 3, minimum, and maximum. Categorical variables will be summarized using number (%). Characteristics will be summarized for eyes with and without events.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The MAH must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (if applicable), and documentation of IRB/EC and governmental approval/notification (if required).

The MAH shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Vestrum will comply with the MAH procedures regarding content, archiving and records management of process documents.

Retention of Records

Archiving at the study site has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by the MAH for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the MAH. Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Adverse events may be underreported in EHRs, which may lead to an underestimate of the incidence. Furthermore, any inaccuracies in the ICD-9/10-CM diagnosis codes recorded in the EHR can lead to misclassification of the event. The codes and combinations of codes used to identify RV, RV with RO, and IOI (including RV) with RO may not represent all possible diagnosis codes used to record these conditions, which may lead to missed cases of adverse events. In addition, for codes that are present over the long-term in the EHR, it is not known whether these codes represent an ongoing condition or whether they are carryover codes that were never removed. Thus, it is not known whether that condition is still active.

Given the rarity of RV, RV with RO, and IOI (including RV) with RO, the estimates may be imprecise. The estimates may also be impacted by reporting bias. Retina specialists may be more vigilant in reporting the adverse events of interest after increased awareness of these events following brolucizumab launch in October 2019, where the occurrence of these events after brolucizumab treatment were identified and widely reported (American Society of Retina Specialists 2020, Khanani et al. 2021). As described earlier, although data are available from 1 January 2014 to 30 September 2023 within the Vestrum database, the analyses may consider alternative time periods to account for potential surveillance or reporting bias due to increased awareness of these events following brolucizumab launch.

The analysis only includes the eyes of patients who are seen at private retina specialist clinics in the United States. This limits the generalizability of the study results. Results may not be generalizable to eyes of patients seen at non-private institutions (e.g., academic medical centers), eyes of patients in countries beyond the US, and eyes of patients seen by non-retina specialists.

8.10 OTHER ASPECTS

Not applicable.

9. PROTECTION OF HUMAN PATIENTS

9.1 INFORMED CONSENT

For this study, it is not necessary, or possible/practical to obtain informed consent for use of secondary data. However certain precautions will be taken, including:

- Ensuring data are anonymised
- Ensuring final analysis data are anonymised
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled

9.2 CONFIDENTIALITY

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, MAH monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9.3 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiology Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a voluntary non-mandated Non-Interventional Post Authorization Safety Study (NI-PASS) involving the use of secondary data and the reporting of adverse reactions in the form of Individual Case Safety Reports (ICSRs) is not required.

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim safety analyses and in the final study report and final publication.

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of NI-PASS, the marketing authorization holder is dedicated to openly providing information on the NI-PASS to healthcare professionals and to the

public, both at scientific congresses and in peer-reviewed journals. The marketing authorization holder will comply with all requirements for publication of study results.

12. REFERENCES

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

None