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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab

Trial Indication(s)

Neovascular age-related macular degeneration

Protocol Number

CRTH258A1401

Protocol Title

A 52-weeks observational study to evaluate the safety of brolucizumab (6mg) in patients with neovascular age-related macular degeneration (nAMD)

Clinical Trial Phase

Phase IV

Phase of Drug Development

Approval Phase

Study Start/End Dates

Study Start Date: November 16, 2020 (Actual)
Primary Completion Date: November 10, 2022 (Actual)
Study Completion Date: November 10, 2022 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This study is a prospective, uncontrolled, central registration system, multicenter, domestic observational study (special drug-use surveillance) to evaluate the safety of 52-week clinical treatment with Beovu in nAMD patients.
Patient registration was electronic data capture (EDC)-based and adopted a central registration system.
After written consent was provided prior to the start of brolucizumab administration, the investigator recorded necessary information on all patients having provided consent on the EDC registration screen to register them.
The observational period was 1 year (52 weeks) from the first brolucizumab administration in the primary treated eye. However, if brolucizumab was discontinued in the primary treated eye and if the treatment was discontinued less than 52 weeks observation period, the observation period was to be up to 90 days after the last dose of this drug. This was set in order to collect data as much as possible based on the clinical effect of the drug. If 30 days after the last dose of this drug in a discontinued patient exceeded 52 weeks of the observation period, the patient was to be monitored for adverse events until 30 days after the last dose of this drug and reported as adverse event.
Eyes treated with brolucizumab first were denoted as primary treated eyes and the contralateral eyes, if treated, were denoted as secondary treated eyes. Ocular results were evaluated separately for the primary treated eyes and the secondary treated eyes with the evaluation in the primary treated eyes being primary.

Centers

Japan(67)

Objectives:

Primary objective

- To investigate the occurrence of adverse events occurring in the eyes on therapy and other parts of the body (non-ocular) of nAMD patients with subfoveal CNV clinically treated with brolucizumab and evaluate its safety

Secondary objectives

- To evaluate the safety of brolucizumab in clinical use in detail when it is administered to nAMD patients with subfoveal CNV

- To investigate data on the administration of brolucizumab in clinical use in nAMD patients with subfoveal CNV

Test Product (s), Dose(s), and Mode(s) of Administration

Intravitreal injection of brolucizumab 6mg

Statistical Methods

In this study, only case report forms (CRF) data recorded by the investigator were used for statistical analyses.
All statistical analyses were performed by Novartis Pharma and EPS Corporation using SAS version 9.4 or higher. The statistical analyses of the study data were primarily descriptive. Data used in the analysis were, in principle, information before treatment with Beovu and data during the observation period specified in the protocol. However, this does not apply to the outcome/date of outcome of the adverse events.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. Patients must provide written consent to cooperate in this study before treatment with Beovu kit for intravitreal injection
2. Patients using Beovu kit for intravitreal injection for the first time for the following indication:
• Indication: age-related macular degeneration with subfoveal choroidal neovascularization

Exclusion Criteria:
1. Patients with a history of treatment with a drug containing the same ingredient (brolucizumab; investigational drug or post-marketing clinical study drug) as Beovu kit for intravitreal injection

Participant Flow Table

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Table 10-1 Patient composition

Analysis population	n
Registration-confirmed population	329
Patients with CRF not collected	0
Not collectable*	0
CRF collection ongoing (including re-investigation)	0
CRF-locked population	329
Patients excluded from safety analysis	1
Beovu not administered	1
Start date of Beovu unknown/not recorded	1
Safety analysis set	328

Table 10-5 Breakdown of patients who discontinued treatment with Beovu (safety analysis population)

Discontinuation/reason for discontinuation	Safety analysis set N=328 n (%)
Discontinuation	93 (28.35)
Adverse events (including worsening of nAMD and worsening of complications)	40 (12.20)
Lost to follow-up (including no visit and hospital change)	18 (5.49)
Insufficient response	14 (4.27)
Patient/family decision	12 (3.66)
Other aspects	6 (1.83)
Achievement of therapeutic goal	3 (0.91)

Patients for whom CRF cannot be collected.
*Patients excluded from the safety analysis set who had multiple reasons for exclusion were included in each reason for exclusion for tabulation.

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Baseline Characteristics

Table 10-2 Demographic and disease characteristics (safety analysis set)

Background factors	Safety analysis set N=328
Sex - n (%)	
Male	238 (72.56)
Female	90 (27.44)
Age (years)	
Sample size	328
Mean (SD)	76.0 (7.99)
Median	77.0
Min - Max	51 - 99
Age (elderly) - n (%)	
< 65 years	29 (8.84)
≥ 65 years	299 (91.16)
Age (late elderly) - n (%)	
< 75 years	132 (40.24)
≥ 75 years	196 (59.76)
Age (years) - n (%)	
< 65 years	29 (8.84)
≥ 65 to < 75 years	103 (31.40)
≥ 75 to < 85 years	151 (46.04)
≥ 85 years	45 (13.72)
Reason for Beovu use - n (%)	
nAMD	328 (100)
Other aspects	0
History of treatment with a drug containing the same ingredient (brolucizumab) as Beovu - n (%)	
No	328 (100)
Yes	0
Eye with nAMD - n (%)	
Right eye	152 (46.34)
Left eye	143 (43.60)
Both eyes	33 (10.06)

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Background factors	Safety analysis set N=328
Medical history: Dyslipidaemia (hyperlipidaemia, etc.) - n (%)	
No	270 (82.32)
Yes	4 (1.22)
Unknown/not specified	54 (16.46)
Medical history: Diabetes mellitus - n (%)	
No	294 (89.63)
Yes	2 (0.61)
Unknown/not specified	32 (9.76)
Medical history: Autoimmune disorders - n (%)	
No	282 (85.98)
Yes	1 (0.30)
Unknown/not specified	45 (13.72)
Medical history: Cardiovascular disorders - n (%)	
No	279 (85.06)
Yes	13 (3.96)
Unknown/not specified	36 (10.98)
Complication: Dyslipidaemia (hyperlipidaemia, etc.) - n (%)	
No	229 (69.82)
Yes	45 (13.72)
Unknown/not specified	54 (16.46)
Complication: Diabetes mellitus - n (%)	
No	265 (80.79)
Yes	31 (9.45)
Unknown/not specified	32 (9.76)
Complication: Autoimmune disorders - n (%)	
No	278 (84.76)
Yes	5 (1.52)
Unknown/not specified	45 (13.72)
Complication: Cardiovascular disorders - n (%)	
No	264 (80.49)
Yes	28 (8.54)
Unknown/not specified	36 (10.98)
Height (cm)	
Sample size	132
Mean (SD)	161.00 (8.030)
Median	162.00
Min - Max	138.0 - 180.5

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Background factors	Safety analysis set N=328
Weight (kg)	
Sample size	129
Mean (SD)	60.11 (11.011)
Median	60.00
Min - Max	38.6 - 103.1
BMI (kg/m^2)	
Sample size	129
Mean (SD)	23.08 (3.364)
Median	22.88
Min - Max	15.3 - 39.7
BMI category - n (%)	
< 25 kg/m^2	94 (28.66)
≥ 25 kg/m^2	35 (10.67)
Unknown/not specified	199 (60.67)
Smoking history - n (%)	
Does not smoke	103 (31.40)
Previously smoked	84 (25.61)
Currently smoking	22 (6.71)
Unknown/not specified	119 (36.28)

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Table 10-3 Demographic and disease characteristics by treated eye (safety analysis set)

	Safety analysis set N=328	
Background factors	Primary treated eye m=328	Secondary treated eye m=12
nAMD subtype - n (%)		
Typical AMD	145 (44.21)	4 (33.33)
RAP	5 (1.52)	1 (8.33)
PCV	147 (44.82)	5 (41.67)
Unknown/not specified	31 (9.45)	2 (16.67)
CNV lesion subtype - n (%)		
Predominantly Classic CNV	50 (15.24)	2 (16.67)
Minimally Classic CNV	12 (3.66)	2 (16.67)
Occult with no Classic CNV	170 (51.83)	3 (25.00)
Unknown/not specified	96 (29.27)	5 (41.67)

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Background factors	Safety analysis set N=328	
	Primary treated eye	Secondary treated eye
	m=328	m=12
History of VEGF inhibitor treatment* - n (%)		
No	102 (31.10)	6 (50.00)
Yes	226 (68.90)	6 (50.00)
History of VEGF inhibitor treatment*: Lucentis/ranibizumab -n (%)		
No	311 (94.82)	11 (91.67)
Yes	17 (5.18)	1 (8.33)
History of VEGF inhibitor treatment*: Eylea/aflibercept - n (%)		
No	119 (36.28)	7 (58.33)
Yes	209 (63.72)	5 (41.67)
Number of days since switching from other VEGF inhibitors* (days)		
Sample size	218	5
Mean (SD)	63.3 (33.06)	47.6 (22.71)
Median	57.0	57.0
Min - Max	17 - 171	15 - 71
Number of days since switching from other VEGF inhibitors* ** (days) - n (%)		
Sample size	226	6
< 28 years	3 (1.33)	1 (16.67)
≥ 28 years	215 (95.13)	4 (66.67)
Unknown/not specified	8 (3.54)	1 (16.67)
Reason for switching from other VEGF inhibitors* ** - n (%)		
Sample size	226	6
Insufficient response	172 (76.11)	4 (66.67)
Safety problem	1 (0.44)	0
Prolongation of treatment interval	48 (21.24)	2 (33.33)
Other aspects	5 (2.21)	0
History of photodynamic therapy (PDT)* - n (%)		
No	321 (97.87)	12 (100)
Yes	7 (2.13)	0
Complication with glaucoma (POAG) - n (%)		
No	320 (97.56)	11 (91.67)
Yes	8 (2.44)	1 (8.33)
Complication with glaucoma (NTG) - n (%)		
No	318 (96.95)	12 (100)
Yes	10 (3.05)	0

	Safety analysis set N=328	
	Primary treated eye	Secondary treated eye
Background factors	m=328	m=12
Complication with ocular hypertension - n (%)		
No	321 (97.87)	12 (100)
Yes	7 (2.13)	0
History of endophthalmitis - n (%)		
No	327 (99.70)	12 (100)
Yes	1 (0.30)	0
History of intraocular inflammation - n (%)		
No	326 (99.39)	12 (100)
Yes	2 (0.61)	0

The denominator for the proportion was the number of patients with the study eye (m).
* Prior therapies were limited to those used within 6 months before the administration in the primary treated eye.
** The denominator of the proportion was the patients with a history of treatment with VEGF inhibitors.

Primary Outcome Result(s)

1. Numbers and proportions of patients with adverse events in the eyes on therapy in the observation period

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Table 10-6 Occurrence of adverse events in the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=328 Primary treated eye m=328 n (%)	Secondary treated eye m=12 n (%)
Total	56 (17.07)	1 (8.33)
Infections and infestations	1 (0.30)	0
Chorioretinitis	1 (0.30)	0
Eye disorders	55 (16.77)	1 (8.33)
Eye inflammation	13 (3.96)	0
Iritis	10 (3.05)	0
Retinal vasculitis	8 (2.44)	0
Vitreous opacity	8 (2.44)	0
Retinal haemorrhage	6 (1.83)	0
Cataract	5 (1.52)	1 (8.33)
Uveitis	5 (1.52)	0
Vitreous floaters	3 (0.91)	0
Vitritis	3 (0.91)	0
Keratic precipitates	3 (0.91)	0
Retinal vascular occlusion	2 (0.61)	0
Anterior chamber inflammation	2 (0.61)	0
Age-related macular degeneration	2 (0.61)	0
Retinal perivascular sheathing	2 (0.61)	0
Retinal occlusive vasculitis	2 (0.61)	0
Asthenopia	1 (0.30)	0
Vision blurred	1 (0.30)	0
Visual acuity reduced	1 (0.30)	0
Vitreal cells	1 (0.30)	0
Non-infectious endophthalmitis	1 (0.30)	0
General disorders and administration site conditions	1 (0.30)	0
Therapeutic response decreased	1 (0.30)	0
Investigations	1 (0.30)	0
Intraocular pressure increased	1 (0.30)	0

SOC: If multiple PTs in the same SOC occurred in the same treated eye, these were counted as 1 patient.

PT: If the same PT occurred multiple times in the same treated eye, these were counted as 1 patient.
SOC is listed in the internationally agreed order, PT is listed in descending order of incidence in the primary treated eye -> order of the PT code, then in descending order of incidence in the secondary treated eye -> order of the PT code.
The denominator for the proportion was the number of patients with the study eye (m).

2. Numbers and proportions of patients with adverse events in other parts of the body (non-ocular) in the observation period

Table 10-7 Occurrence of adverse events in other parts of the body (non-ocular) (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=328 n (%)
Total	2 (0.61)
Nervous system disorders	1 (0.30)
Cerebral infarction	1 (0.30)
General disorders and administration site conditions	1 (0.30)
Death	1 (0.30)

Secondary Outcome Result(s)

1. Numbers and proportions of patients with serious adverse events (SAEs) and adverse reactions (ADRs) in the eyes on therapy in the observation period

Table 10-8 Occurrence of serious adverse events in the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=328 Primary treated eye m=328 n (%)	Safety analysis set N=328 Secondary treated eye m=12 n (%)
Total	9 (2.74)	0
Eye disorders	9 (2.74)	0
Retinal vasculitis	3 (0.91)	0
Cataract	2 (0.61)	0
Retinal haemorrhage	2 (0.61)	0
Retinal vascular occlusion	2 (0.61)	0
Eye inflammation	1 (0.30)	0
Iritis	1 (0.30)	0

SOC: If multiple PTs in the same SOC occurred in the same treated eye, these were counted as 1 patient.
PT: If the same PT occurred multiple times in the same treated eye, these were counted as 1 patient.
SOC is listed in the internationally agreed order, PT is listed in descending order of incidence in the primary treated eye -> order of the PT code, then in descending order of incidence in the secondary treated eye -> order of the PT code.
The denominator for the proportion was the number of patients with the study eye (m).

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Table 10-10 Occurrence of adverse reactions in the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=328 Primary treated eye m=328 n (%)	 Secondary treated eye m=12 n (%)
Total	47 (14.33)	0
Infections and infestations	1 (0.30)	0
Chorioretinitis	1 (0.30)	0
Eye disorders	46 (14.02)	0
Eye inflammation	13 (3.96)	0
Iritis	10 (3.05)	0
Retinal vasculitis	8 (2.44)	0
Vitreous opacity	8 (2.44)	0
Uveitis	5 (1.52)	0
Vitreous floaters	3 (0.91)	0
Vitritis	3 (0.91)	0
Keratic precipitates	3 (0.91)	0
Retinal haemorrhage	2 (0.61)	0
Retinal vascular occlusion	2 (0.61)	0
Anterior chamber inflammation	2 (0.61)	0
Retinal perivascular sheathing	2 (0.61)	0
Retinal occlusive vasculitis	2 (0.61)	0
Asthenopia	1 (0.30)	0
Vision blurred	1 (0.30)	0
Visual acuity reduced	1 (0.30)	0
Age-related macular degeneration	1 (0.30)	0
Vitreal cells	1 (0.30)	0
Non-infectious endophthalmitis	1 (0.30)	0
General disorders and administration site conditions	1 (0.30)	0
Therapeutic response decreased	1 (0.30)	0
Investigations	1 (0.30)	0
Intraocular pressure increased	1 (0.30)	0

SOC: If multiple PTs in the same SOC occurred in the same treated eye, these were counted as 1 patient.
PT: If the same PT occurred multiple times in the same treated eye, these were counted as 1 patient.
SOC is listed in the internationally agreed order, PT is listed in descending order of incidence in the primary treated eye -> order of the PT code, then in descending order of incidence in the secondary treated eye -> order of the PT code.
The denominator for the proportion was the number of patients with the study eye (m).

2. Numbers and proportions of patients with SAEs and ADRs in other parts of the body (non-ocular) in the observation period

Table 10-9 Occurrence of serious adverse events in other parts of the body (non-ocular) (by SOC and PT) (safety analysis set)

	Safety analysis set
SOC	N=328
PT	n (%)
Total	2 (0.61)
Nervous system disorders	1 (0.30)
Cerebral infarction	1 (0.30)
General disorders and administration site conditions	1 (0.30)
Death	1 (0.30)

SOC: If multiple PTs in the same SOC occurred in the same patient, these were counted as 1 patient.
PT: If the same PT occurred multiple times in the same patient, these were counted as 1 patient.
SOC is listed in the internationally agreed order, PT is listed in descending order of incidence in the primary treated eye -> order of the PT code.

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Table 10-11 Occurrence of adverse reactions in other parts of the body (non-ocular) (by SOC and PT) (safety analysis set)

	Safety analysis set
SOC	N=328
PT	n (%)
Total	1 (0.30)
Nervous system disorders	1 (0.30)
Cerebral infarction	1 (0.30)

SOC: If multiple PTs in the same SOC occurred in the same patient, these were counted as 1 patient.
PT: If the same PT occurred multiple times in the same patient, these were counted as 1 patient.
SOC is listed in the internationally agreed order, PT is listed in descending order of incidence in the primary treated eye -> order of the PT code.

Table 10-12 Occurrence of serious adverse reactions the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=328 Primary treated eye m=328 n (%)	Secondary treated eye m=12 n (%)
Total	5 (1.52)	0
Eye disorders	5 (1.52)	0
Retinal vasculitis	3 (0.91)	0
Retinal vascular occlusion	2 (0.61)	0
Eye inflammation	1 (0.30)	0
Iritis	1 (0.30)	0

SOC: If multiple PTs in the same SOC occurred in the same treated eye, these were counted as 1patient.
PT: If the same PT occurred multiple times in the same treated eye, these were counted as 1 patient.
SOC is listed in the internationally agreed order, PT is listed in descending order of incidence in the primary treated eye -> order of the PT code, then in descending order of incidence in the secondary treated eye -> order of the PT code.
The denominator for the proportion was the number of patients with the study eye (m).

3. Numbers and proportions of patients with adverse events, SAEs, ADRs and serious ADRs corresponding to the safety specifications in the observation period

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Table 10-15 Occurrence of safety specifications (adverse events and adverse reactions) (by PT) (safety analysis set)

Safety specifications PT	Safety analysis set N=328					
	Adverse events			Adverse reactions		
	Primary treated eye m=328 n (%)	Secondary treated eye m=12 n (%)	Other parts of the body (non-ocular) m=328 n (%)	Primary treated eye m=328 n (%)	Secondary treated eye m=12 n (%)	Other parts of the body (non-ocular) m=328 n (%)
Total	40 (12.20)	0	1 (0.30)	40 (12.20)	0	1 (0.30)
Intraocular inflammation	39 (11.89)	0	-	39 (11.89)	0	-
Eye inflammation	13 (3.96)	0	-	13 (3.96)	0	-
Iritis	10 (3.05)	0	-	10 (3.05)	0	-
Retinal vasculitis	8 (2.44)	0	-	8 (2.44)	0	-
Uveitis	5 (1.52)	0	-	5 (1.52)	0	-
Vitritis	3 (0.91)	0	-	3 (0.91)	0	-
Keratic precipitates	3 (0.91)	0	-	3 (0.91)	0	-
Anterior chamber inflammation	2 (0.61)	0	-	2 (0.61)	0	-
Retinal occlusive vasculitis	2 (0.61)	0	-	2 (0.61)	0	-
Chorioretinitis	1 (0.30)	0	-	1 (0.30)	0	-
Endophthalmitis	1 (0.30)	0	-	1 (0.30)	0	-
Non-infectious endophthalmitis	1 (0.30)	0	-	1 (0.30)	0	-
Intraocular pressure increased	1 (0.30)	0	-	1 (0.30)	0	-
Intraocular pressure increased	1 (0.30)	0	-	1 (0.30)	0	-
Retinal vasculitis and retinal vascular occlusion	11 (3.35)	0	-	11 (3.35)	0	-
Retinal vasculitis	8 (2.44)	0	-	8 (2.44)	0	-
Retinal vascular occlusion	2 (0.61)	0	-	2 (0.61)	0	-
Retinal occlusive vasculitis	2 (0.61)	0	-	2 (0.61)	0	-
Non-ocular arterial thromboembolic events	-	-	1 (0.30)	-	-	1 (0.30)
Cerebral infarction	-	-	1 (0.30)	-	-	1 (0.30)

Safety specifications: For ocular events, if multiple PTs in the same safety specification occurred in the same treated eye, these were counted as 1 patient.
For events in other parts of the body, if multiple PTs in the same safety specification occurred in the same patient, these were counted as 1 patient.
PT: For ocular events, if the same PT occurred multiple times in the same treated eye, these were counted as 1 patient.
For events in other parts of the body, if the same PT occurred multiple times in the same patient, these were counted as 1 patient.
For ocular events, PT is listed in descending order of incidence in the adverse event column for the primary treated eye -> order of the PT code, then in descending order of incidence in the adverse event column for the secondary treated eye -> order of the PT code.
The PT that occurred in the other parts of the body are listed in descending order of incidence in the adverse event column -> order of the PT code.
The denominator for proportion was the number of patients with the study eye for ocular events, and the number of patients (m) in the safety analysis set for events that occurred in other parts of the body.

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Table 10-16 Occurrence of safety specifications (adverse reactions and serious adverse reactions) (by PT) (safety analysis set)

	Safety analysis set N=328					
	Adverse reactions			Serious adverse reactions		
Safety specifications PT	Primary treated eye m=328 n (%)	Secondary treated eye m=12 n (%)	Other parts of the body (non-ocular) m=328 n (%)	Primary treated eye m=328 n (%)	Secondary treated eye m=12 n (%)	Other parts of the body (non-ocular) m=328 n (%)
Total	40 (12.20)	0	1 (0.30)	5 (1.52)	0	1 (0.30)
Intraocular inflammation	39 (11.89)	0	-	4 (1.22)	0	-
Eye inflammation	13 (3.96)	0	-	1 (0.30)	0	-
Iritis	10 (3.05)	0	-	1 (0.30)	0	-
Retinal vasculitis	8 (2.44)	0	-	3 (0.91)	0	-
Uveitis	5 (1.52)	0	-	0	0	-
Vitritis	3 (0.91)	0	-	0	0	-
Keratic precipitates	3 (0.91)	0	-	0	0	-
Anterior chamber inflammation	2 (0.61)	0	-	0	0	-
Retinal occlusive vasculitis	2 (0.61)	0	-	0	0	-
Chorioretinitis	1 (0.30)	0	-	0	0	-
Endophthalmitis	1 (0.30)	0	-	0	0	-
Non-infectious endophthalmitis	1 (0.30)	0	-	0	0	-
Intraocular pressure increased	1 (0.30)	0	-	0	0	-
Intraocular pressure increased	1 (0.30)	0	-	0	0	-
Retinal vasculitis and retinal vascular occlusion	11 (3.35)	0	-	4 (1.22)	0	-
Retinal vasculitis	8 (2.44)	0	-	3 (0.91)	0	-
Retinal vascular occlusion	2 (0.61)	0	-	2 (0.61)	0	-
Retinal occlusive vasculitis	2 (0.61)	0	-	0	0	-
Non-ocular arterial thromboembolic events	-	-	1 (0.30)	-	-	1 (0.30)
Cerebral infarction	-	-	1 (0.30)	-	-	1 (0.30)

Safety specifications: For ocular events, if multiple PTs in the same safety specification occurred in the same treated eye, these were counted as 1 patient.
For events in other parts of the body, if multiple PTs in the same safety specification occurred in the same patient, these were counted as 1 patient.
PT: For ocular events, if the same PT occurred multiple times in the same treated eye, these were counted as 1 patient.
For events in other parts of the body, if the same PT occurred multiple times in the same patient, these were counted as 1 patient.
For ocular events, PT is listed in descending order of incidence in the adverse event column for the primary treated eye -> order of the PT code, then in descending order of incidence in the adverse event column for the secondary treated eye -> order of the PT code.
The PT that occurred in the other parts of the body are listed in descending order of incidence in the adverse event column -> order of the PT code.
The denominator for proportion was the number of patients with the study eye for ocular events, and the number of patients (m) in the safety analysis set for events that occurred in other parts of the body.

4. Incidences of adverse events by risk factor of the safety specifications (primary treated eyes only)

Table SubGroup_T002: Number and Proportion of Patients with Safety Specifications (Adverse Events) in the Primary Treated Eye, and Odds Ratio in Each Category by Patient Factor (Safety Analysis Set)".

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Safety specification: Intraocular inflammation

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	39 (11.89)	--
Gender			
Male	238	24 (10.08)	REF
Female	90	15 (16.67)	1.78 (0.89, 3.58)
Age category			
< 65 years	29	5 (17.24)	REF
≥ 65 to < 75 years	103	17 (16.50)	0.95 (0.32, 2.84)
≥ 75 to < 85 years	151	14 (9.27)	0.49 (0.16, 1.49)
≥ 85 years	45	3 (6.67)	0.34 (0.08, 1.56)
Prior VEGF inhibitor therapy*			
No	102	6 (5.88)	REF
Yes	226	33 (14.60)	2.74 (1.11, 6.75)
Prior VEGF inhibitor therapy*: Lucentis / ranibizumab			
No	311	36 (11.58)	REF
Yes	17	3 (17.65)	1.64 (0.45, 5.97)
Prior VEGF inhibitor therapy*: Eylea / aflibercept			
No	119	9 (7.56)	REF
Yes	209	30 (14.35)	2.05 (0.94, 4.48)
Prior photodynamic therapy (PDT)*			
No	321	39 (12.15)	REF
Yes	7	0	- (NE, NE)
Past history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	270	32 (11.85)	REF
Yes	4	1 (25.00)	2.48 (0.25, 24.56)
Unknown/not reported	54	6 (11.11)	--
Past history‡ Diabetes mellitus			
No	294	35 (11.90)	REF
Yes	2	0	- (NE, NE)
Unknown/not reported	32	4 (12.50)	--
Past history: Autoimmune disease			
No	282	32 (11.35)	REF
Yes	1	0	- (NE, NE)
Unknown/not reported	45	7 (15.56)	--

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Safety specification: Intraocular inflammation

Background factors	m	n (%)	Odds ratio (95% CI)
Past history: Cardiovascular disease			
No	279	32 (11.47)	REF
Yes	13	2 (15.38)	1.40 (0.30, 6.62)
Unknown/not reported	36	5 (13.89)	--
Present history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	229	22 (9.61)	REF
Yes	45	11 (24.44)	3.04 (1.35, 6.84)
Unknown/not reported	54	6 (11.11)	--
Present history: Diabetes mellitus			
No	265	32 (12.08)	REF
Yes	31	3 (9.68)	0.78 (0.22, 2.71)
Unknown/not reported	32	4 (12.50)	--
Present history: Autoimmune disease			
No	278	31 (11.15)	REF
Yes	5	1 (20.00)	1.99 (0.22, 18.39)
Unknown/not reported	45	7 (15.56)	--
Present history: Cardiovascular disease			
No	264	31 (11.74)	REF
Yes	28	3 (10.71)	0.90 (0.26, 3.16)
Unknown/not reported	36	5 (13.89)	--
Smoking history			
Non-smoker	103	14 (13.59)	REF
Former smoker	84	14 (16.67)	1.27 (0.57, 2.84)
Current smoker	22	2 (9.09)	0.64 (0.13, 3.02)
Unknown/not reported	119	9 (7.56)	--
Concurrent glaucoma (POAG)			
No	320	39 (12.19)	REF
Yes	8	0	- (NE, NE)
Concurrent glaucoma (NTG)			
No	318	39 (12.26)	REF
Yes	10	0	- (NE, NE)
Prior ocular hypertension			
No	321	39 (12.15)	REF
Yes	7	0	- (NE, NE)

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Safety specification: Intraocular inflammation

Background factors	m	n (%)	Odds ratio (95% CI)
Prior endophthalmitis			
No	327	38 (11.62)	REF
Yes	1	1 (100)	- (NE, NE)
Prior intraocular inflammation			
No	326	38 (11.66)	REF
Yes	2	1 (50.00)	7.58 (0.46, 123.67)
BMI category			
< 25 kg/m^2	94	12 (12.77)	REF
≥ 25 kg/m^2	35	5 (14.29)	1.14 (0.37, 3.50)
Unknown/not reported	199	22 (11.06)	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category
n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

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Safety specification: Endophthalmitis

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	1 (0.30)	--
Gender			
Male	238	1 (0.42)	REF
Female	90	0	- (NE, NE)
Age category			
< 65 years	29	0	REF
≥ 65 to < 75 years	103	1 (0.97)	- (NE, NE)
≥ 75 to < 85 years	151	0	- (NE, NE)
≥ 85 years	45	0	- (NE, NE)
Prior VEGF inhibitor therapy*			
No	102	1 (0.98)	REF
Yes	226	0	- (NE, NE)
Prior VEGF inhibitor therapy*: Lucentis / ranibizumab			
No	311	1 (0.32)	REF
Yes	17	0	- (NE, NE)
Prior VEGF inhibitor therapy*: Eylea / aflibercept			
No	119	1 (0.84)	REF
Yes	209	0	- (NE, NE)
Prior photodynamic therapy (PDT)*			
No	321	1 (0.31)	REF
Yes	7	0	- (NE, NE)
Past history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	270	1 (0.37)	REF
Yes	4	0	- (NE, NE)
Unknown/not reported	54	0	--
Past history: Diabetes mellitus			
No	294	1 (0.34)	REF
Yes	2	0	- (NE, NE)
Unknown/not reported	32	0	--
Past history: Autoimmune disease			
No	282	1 (0.35)	REF
Yes	1	0	- (NE, NE)
Unknown/not reported	45	0	--

NOVARTIS

Safety specification: Endophthalmitis			
Background factors	m	n (%)	Odds ratio (95% CI)
Past history: Cardiovascular disease			
No	279	1 (0.36)	REF
Yes	13	0	- (NE, NE)
Unknown/not reported	36	0	--
Present history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	229	1 (0.44)	REF
Yes	45	0	- (NE, NE)
Unknown/not reported	54	0	--
Present history: Diabetes mellitus			
No	265	0	REF
Yes	31	1 (3.23)	- (NE, NE)
Unknown/not reported	32	0	--
Present history: Autoimmune disease			
No	278	1 (0.36)	REF
Yes	5	0	- (NE, NE)
Unknown/not reported	45	0	--
Present history: Cardiovascular disease			
No	264	1 (0.38)	REF
Yes	28	0	- (NE, NE)
Unknown/not reported	36	0	--
Smoking history			
Non-smoker	103	0	REF
Former smoker	84	0	- (NE, NE)
Current smoker	22	0	- (NE, NE)
Unknown/not reported	119	1 (0.84)	--
Concurrent glaucoma (POAG)			
No	320	1 (0.31)	REF
Yes	8	0	- (NE, NE)
Concurrent glaucoma (NTG)			
No	318	1 (0.31)	REF
Yes	10	0	- (NE, NE)
Prior ocular hypertension			
No	321	1 (0.31)	REF
Yes	7	0	- (NE, NE)

NOVARTIS

Safety specification: Endophthalmitis			
Background factors	m	n (%)	Odds ratio (95% CI)
Prior endophthalmitis			
No	327	1 (0.31)	REF
Yes	1	0	- (NE, NE)
Prior intraocular inflammation			
No	326	1 (0.31)	REF
Yes	2	0	- (NE, NE)
BMI category			
< 25 kg/m^2	94	0	REF
≥ 25 kg/m^2	35	0	- (NE, NE)
Unknown/not reported	199	1 (0.50)	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category
n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

NOVARTIS

Safety specification: Intraocular pressure increased

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	1 (0.30)	--
Gender			
Male	238	1 (0.42)	REF
Female	90	0	- (NE, NE)
Age category			
< 65 years	29	1 (3.45)	REF
≥ 65 to < 75 years	103	0	- (NE, NE)
≥ 75 to < 85 years	151	0	- (NE, NE)
≥ 85 years	45	0	- (NE, NE)
Prior VEGF inhibitor therapy*			
No	102	0	REF
Yes	226	1 (0.44)	- (NE, NE)
Prior VEGF inhibitor therapy*: Lucentis / ranibizumab			
No	311	1 (0.32)	REF
Yes	17	0	- (NE, NE)
Prior VEGF inhibitor therapy*: Eylea / aflibercept			
No	119	0	REF
Yes	209	1 (0.48)	- (NE, NE)
Prior photodynamic therapy (PDT)*			
No	321	1 (0.31)	REF
Yes	7	0	- (NE, NE)
Past history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	270	1 (0.37)	REF
Yes	4	0	- (NE, NE)
Unknown/not reported	54	0	--
Past history: Diabetes mellitus			
No	294	1 (0.34)	REF
Yes	2	0	- (NE, NE)
Unknown/not reported	32	0	--
Past history: Autoimmune disease			
No	282	1 (0.35)	REF
Yes	1	0	- (NE, NE)
Unknown/not reported	45	0	--

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Safety specification: Intraocular pressure increased			
Background factors	m	n (%)	Odds ratio (95% CI)
Past history: Cardiovascular disease			
No	279	1 (0.36)	REF
Yes	13	0	- (NE, NE)
Unknown/not reported	36	0	--
Present history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	229	1 (0.44)	REF
Yes	45	0	- (NE, NE)
Unknown/not reported	54	0	--
Present history: Diabetes mellitus			
No	265	1 (0.38)	REF
Yes	31	0	- (NE, NE)
Unknown/not reported	32	0	--
Present history: Autoimmune disease			
No	278	1 (0.36)	REF
Yes	5	0	- (NE, NE)
Unknown/not reported	45	0	--
Present history: Cardiovascular disease			
No	264	1 (0.38)	REF
Yes	28	0	- (NE, NE)
Unknown/not reported	36	0	--
Smoking history			
Non-smoker	103	0	REF
Former smoker	84	1 (1.19)	- (NE, NE)
Current smoker	22	0	- (NE, NE)
Unknown/not reported	119	0	--
Concurrent glaucoma (POAG)			
No	320	1 (0.31)	REF
Yes	8	0	- (NE, NE)
Concurrent glaucoma (NTG)			
No	318	1 (0.31)	REF
Yes	10	0	- (NE, NE)
Prior ocular hypertension			
No	321	1 (0.31)	REF
Yes	7	0	- (NE, NE)

NOVARTIS

Safety specification: Intraocular pressure increased

Background factors	m	n (%)	Odds ratio (95% CI)
Prior endophthalmitis			
No	327	1 (0.31)	REF
Yes	1	0	- (NE, NE)
Prior intraocular inflammation			
No	326	1 (0.31)	REF
Yes	2	0	- (NE, NE)
BMI category			
< 25 kg/m^2	94	0	REF
≥ 25 kg/m^2	35	0	- (NE, NE)
Unknown/not reported	199	1 (0.50)	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category; n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

Safety specification: Retinal pigment epithelial tear

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	0	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category; n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

Safety specification: Retinal detachment and retinal tear

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	0	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category
n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

Safety specification: Embolus retinal artery events

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	0	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category
n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

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Safety specification: Retinal vasculitis and retinal vascular occlusion

Background factors	m	n (%)	Odds ratio (95% CI)
Safety analysis set	328	11 (3.35)	--
Gender			
Male	238	5 (2.10)	REF
Female	90	6 (6.67)	3.33 (0.99, 11.19)
Age category			
< 65 years	29	1 (3.45)	REF
≥ 65 to < 75 years	103	1 (0.97)	0.27 (0.02, 4.53)
≥ 75 to < 85 years	151	7 (4.64)	1.36 (0.16, 11.50)
≥ 85 years	45	2 (4.44)	1.30 (0.11, 15.05)
Prior VEGF inhibitor therapy*			
No	102	1 (0.98)	REF
Yes	226	10 (4.42)	4.68 (0.59, 37.02)
Prior VEGF inhibitor therapy*: Lucentis / ranibizumab			
No	311	11 (3.54)	REF
Yes	17	0	- (NE, NE)
Prior VEGF inhibitor therapy*: Eylea / aflibercept			
No	119	1 (0.84)	REF
Yes	209	10 (4.78)	5.93 (0.75, 46.90)
Prior photodynamic therapy (PDT)*			
No	321	11 (3.43)	REF
Yes	7	0	- (NE, NE)
Past history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	270	10 (3.70)	REF
Yes	4	0	- (NE, NE)
Unknown/not reported	54	1 (1.85)	--
Past history: Diabetes mellitus			
No	294	11 (3.74)	REF
Yes	2	0	- (NE, NE)
Unknown/not reported	32	0	--
Past history: Autoimmune disease			
No	282	10 (3.55)	REF
Yes	1	0	- (NE, NE)
Unknown/not reported	45	1 (2.22)	--

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Safety specification: Retinal vasculitis and retinal vascular occlusion

Background factors	m	n (%)	Odds ratio (95% CI)
Past history: Cardiovascular disease			
No	279	9 (3.23)	REF
Yes	13	1 (7.69)	2.50 (0.29, 21.36)
Unknown/not reported	36	1 (2.78)	--
Present history: Dyslipidaemia (e.g., hyperlipidaemia)			
No	229	5 (2.18)	REF
Yes	45	5 (11.11)	5.60 (1.55, 20.23)
Unknown/not reported	54	1 (1.85)	--
Present history: Diabetes mellitus			
No	265	10 (3.77)	REF
Yes	31	1 (3.23)	0.85 (0.11, 6.87)
Unknown/not reported	32	0	--
Present history: Autoimmune disease			
No	278	10 (3.60)	REF
Yes	5	0	- (NE, NE)
Unknown/not reported	45	1 (2.22)	--
Present history: Cardiovascular disease			
No	264	9 (3.41)	REF
Yes	28	1 (3.57)	1.05 (0.13, 8.60)
Unknown/not reported	36	1 (2.78)	--
Smoking history			
Non-smoker	103	7 (6.80)	REF
Former smoker	84	3 (3.57)	0.51 (0.13, 2.03)
Current smoker	22	0	- (NE, NE)
Unknown/not reported	119	1 (0.84)	--
Concurrent glaucoma (POAG)			
No	320	11 (3.44)	REF
Yes	8	0	- (NE, NE)
Concurrent glaucoma (NTG)			
No	318	11 (3.46)	REF
Yes	10	0	- (NE, NE)
Prior ocular hypertension			
No	321	11 (3.43)	REF
Yes	7	0	- (NE, NE)

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Safety specification: Retinal vasculitis and retinal vascular occlusion

Background factors	m	n (%)	Odds ratio (95% CI)
Prior endophthalmitis			
No	327	11 (3.36)	REF
Yes	1	0	- (NE, NE)
Prior intraocular inflammation			
No	326	11 (3.37)	REF
Yes	2	0	- (NE, NE)
BMI category			
< 25 kg/m^2	94	6 (6.38)	REF
≥ 25 kg/m^2	35	1 (2.86)	0.43 (0.05, 3.72)
Unknown/not reported	199	4 (2.01)	--

* Only prior therapy used within 6 months before the start of treatment to the first treated eye
Patients with Unknown/not reported are excluded from odds ratio calculation.
m: Number of patients in the applicable category
n: Number of patients with adverse events
REF: Reference for odds ratios
--: Excluded from calculation
NE: not estimable

5. Proportion of patients with VA worsening in the observation period

Table 10-26 VA worsening (safety analysis set)

Applicable patients* N=311	Primary treated eye m=311 n (%)	(95% CI)	Secondary treated eye m=9 n (%)	(95% CI)
During the observation period				
≥ 50% reduction**	46 (14.79)	(11.04, 19.23)	0	-
≥ 75% reduction**	10 (3.22)	(1.55, 5.83)	0	-
Last evaluation point				
≥ 50% reduction	26 (8.36)	(5.53, 12.01)	0	-
≥ 75% reduction	5 (1.61)	(0.52, 3.71)	0	-

* Population: Patients in the safety analysis set who had a record of decimal visual acuity at baseline and at least once during the observation period were included.
** Counted when VA worsening was observed at least once during the observation period.
95% CI was calculated by the Clopper-Pearson method.
The denominator for the proportion was the number of patients with the study eye (m).

6. Data on brolucizumab administration in the induction and maintenance phase during the observation period

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Table 10-4 Beovu administration (safety analysis set)

	Safety analysis set N=328	
	Primary treated eye m=328	Secondary treated eye m=12
Duration of treatment (days)		
Sample size	328	12
Mean (SD)	306.8 (102.16)	265.0 (121.54)
Median	365.0	333.5
Q1 - Q3	292.5 - 365.0	123.5 - 363.0
Min - Max	91 - 365	84 - 365
Treatment duration category - n (%)		
< 3 months	0	2 (16.67)
≥ 3 months to < 6 months	67 (20.43)	2 (16.67)
≥ 6 months to < 9 months	12 (3.66)	0
≥ 9 months to < 12 months	9 (2.74)	4 (33.33)
≥ 12 months	240 (73.17)	4 (33.33)
Dosing frequency (doses)		
Sample size	328	12
Mean (SD)	4.2 (2.08)	2.8 (1.99)
Median	4.0	2.5
Q1 - Q3	3.0 - 6.0	1.0 - 4.5
Min - Max	1 - 8	1 - 6
Dosing frequency category - n (%)		
1 dose	42 (12.80)	5 (41.67)
2 doses	38 (11.59)	1 (8.33)
3 doses	52 (15.85)	2 (16.67)
4 doses	45 (13.72)	1 (8.33)
5 doses	42 (12.80)	1 (8.33)
6 doses	57 (17.38)	2 (16.67)
7 doses	37 (11.28)	0
8 doses	15 (4.57)	0
Duration of the induction phase (days)		
Sample size	328	12
Mean (SD)	30.6 (31.64)	28.6 (30.62)
Median	29.0	17.0
Q1 - Q3	1.0 - 58.5	0.5 - 57.0
Min - Max	0 - 138	0 - 72

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	Safety analysis set N=328	
	Primary treated eye m=328	Secondary treated eye m=12
Induction phase dosing frequency (doses)		
Sample size	328	12
Mean (SD)	1.7 (1.21)	1.7 (1.30)
Median	2.0	1.5
Q1 - Q3	1.0 - 3.0	0.5 - 3.0
Min - Max	0 - 3	0 - 3
Induction phase dosing frequency category - n (%)		
0 doses	72 (21.95)	3 (25.00)
1 dose	89 (27.13)	3 (25.00)
2 doses	32 (9.76)	1 (8.33)
3 doses	135 (41.16)	5 (41.67)
Induction phase dosing frequency category for patients with a history of treatment with other VEGF inhibitors* - n (%)		
Sample size	226	6
0 doses	67 (29.65)	2 (33.33)
1 dose	65 (28.76)	1 (16.67)
2 doses	22 (9.73)	0
3 doses	72 (31.86)	3 (50.00)
Induction phase dosing frequency category for patients without a history of treatment with other VEGF inhibitors* - n (%)		
Sample size	102	6
0 doses	5 (4.90)	1 (16.67)
1 dose	24 (23.53)	2 (33.33)
2 doses	10 (9.80)	1 (16.67)
3 doses	63 (61.76)	2 (33.33)
Duration of the maintenance phase (days)		
Sample size	328	12
Mean (SD)	276.2 (102.57)	236.4 (118.98)
Median	308.0	297.5
Q1 - Q3	251.0 - 364.0	84.5 - 318.5
Min - Max	90 - 365	66 - 363
Maintenance phase dosing frequency (doses)		
Sample size	328	12
Mean (SD)	2.5 (2.01)	1.2 (1.80)
Median	3.0	0.5
Q1 - Q3	0.0 - 4.0	0.0 - 1.5
Min - Max	0 - 8	0 - 6

	Safety analysis set N=328	
	Primary treated eye m=328	Secondary treated eye m=12
Maintenance phase dosing frequency category - n (%)		
0 doses	84 (25.61)	6 (50.00)
1 dose	35 (10.67)	3 (25.00)
2 doses	39 (11.89)	1 (8.33)
3 doses	55 (16.77)	1 (8.33)
4 doses	57 (17.38)	0
5 doses	37 (11.28)	0
6 doses	12 (3.66)	1 (8.33)
7 doses	8 (2.44)	0
8 doses	1 (0.30)	0
Maintenance phase treatment interval** - n (%)		
Number of patients (with at least 1 dose administered in the maintenance phase)	236	-
< 56 day interval present	44 (18.64)	-
< 56 day interval absent	192 (81.36)	-
Treatment interval after 4th dose** - n (%)		
Sample size (with at least 4 doses administered)	196	-
< 56 day interval present	25 (12.76)	-
< 56 day interval absent	171 (87.24)	-

* Prior therapies were limited to those used within 6 months before the administration in the primary treated eye.
** Patients for whom treatment interval (number of days from the previous day of treatment) less than 56 days occurred at least once were classified as “present”.
Unless specified otherwise, the denominator for the proportion was the number of patients with the study eye (m).

Safety Results

Please refer to the primary and secondary results to see the occurrence of adverse events, serious adverse events, adverse drug reactions and serious adverse drug reactions.

All-Cause Mortality

Adverse event leading to death was observed in 1 patient, and the adverse event term was death.

Other Relevant Findings

Not applicable

Conclusion:

The results of this study showed that the adverse events and adverse reactions reported were generally known events, and no notable tendency was observed in the type, seriousness, and outcome of these events. Moreover, no information that require new safety measures was identified.

Date of Clinical Trial Report

14 June 2023