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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab

Trial Indication(s)

Diabetic macular edema

Protocol Number

CRTH258B1401

Protocol Title

Special drug use observational study with Beovu kit for intravitreal injection (DME, CRTH258B1401)

Clinical Trial Phase

Phase IV

Phase of Drug Development

Full Development

Study Start/End Dates

Study Start Date: September 02, 2022 (Actual)
Primary Completion Date: June 29, 2024 (Actual)

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Study Completion Date: June 29, 2024 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This is a primary data collection-based observational special drug-use surveillance to be conducted in accordance with the GPSP ordinance. Observation period was set as 1 year (52 weeks) from the first Beovu administration in the primary treated eye

Centers

Japan(76)

Objectives:

Primary objective

To investigate the occurrence of adverse events occurring in the eyes on therapy and the system (non-ocular) of DME patients clinically treated with Beovu and evaluate its safety

Secondary objectives

- To evaluate the safety of Beovu in clinical use in detail when it is administered to DME patients
- To investigate data on the administration of Beovu in clinical use in DME patients

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

Beovu kit for intravitreal injection 120 mg/mL

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Statistical Methods

The statistical analyses of the study data were primarily descriptive. Data to be used for analyses, in principle, were information obtained before treatment with Beovu and data during the observation period recorded in the protocol except for outcomes of adverse events/dates of outcomes.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Patients must provide written consent to cooperate in this study before the start of treatment with Beovu

2. Patients using Beovu for the first time for the following indication

• Indication: diabetic macular edema

Exclusion Criteria:

1. Patients with a history of treatment with a drug containing the same ingredient (brolucizumab) as Beovu

Participant Flow Table

Patient composition

Analysis population	n
Registration-confirmed population	222
Patients whose CRFs are not collected	0
Not collected*	0
CRFs under collection (including re-investigation)	0

Analysis population	n
CRF-locked population	222
Patients excluded from safety analysis	0
Safety analysis set	222

* Patients for whom CRFs cannot be collected

Number of discontinued patients and reasons for discontinuation (safety analysis set)

	Safety analysis set N=222
Discontinuation/reason for discontinuation	n (%)
Discontinuation	54 (24.3)
Inadequate response	20 (9.0)
Lost to follow-up (including no visit and hospital change)	12 (5.4)
Patient/family decision	9 (4.1)
Adverse events (including worsening of DME and complications)	8 (3.6)
Others	4 (1.8)
Achievement of therapeutic objectives	1 (0.5)

Baseline Characteristics

Demographics and disease characteristics (safety analysis set)

	Safety analysis set N=222
Factors	
Gender – n (%)	
Male	129 (58.1)
Female	93 (41.9)

Factors	Safety analysis set N=222
Age (years)	
Number of patients	222
Mean (SD)	66.7 (10.54)
Median (minimum – maximum)	68.5 (35 - 90)
Age (children/EU) – n (%)	
< 18 years	0
≥ 18 years	222 (100)
Age (elderly) – n (%)	
< 65 years	75 (33.8)
≥ 65 years	147 (66.2)
Age (late elderly) – n (%)	
< 75 years	176 (79.3)
≥ 75 years	46 (20.7)
Age – n (%)	
< 45 years	4 (1.8)
45 to < 55 years	31 (14.0)
55 to < 65 years	40 (18.0)
65 to < 75 years	101 (45.5)
75 to < 85 years	41 (18.5)
≥ 85 years	5 (2.3)
Reason for Beovu use – n (%)	
DME	222 (100)
Others	0
History of treatment with a drug containing the same ingredient (brolucizumab) as Beovu – n (%)	
Absent	222 (100)
Present	0
Eye affected with DME – n (%)	
Right eye	58 (26.1)

Factors	Safety analysis set N=222
Left eye	62 (27.9)
Both eyes	102 (45.9)
Diabetes mellitus – n (%)	
Type 1 diabetes mellitus	10 (4.5)
Type 2 diabetes mellitus	209 (94.1)
Gestational diabetes	0
Other types of diabetes mellitus	3 (1.4)
Concurrent conditions: Dyslipidemia (e.g. hyperlipidemia) – n (%)	
Absent	122 (55.0)
Present	47 (21.2)
Unknown/not recorded	53 (23.9)
Concurrent conditions: Autoimmune disease – n (%)	
Absent	191 (86.0)
Present	1 (0.5)
Unknown/not recorded	30 (13.5)
Concurrent conditions: Cardiovascular disease – n (%)	
Absent	171 (77.0)
Present	22 (9.9)
Unknown/not recorded	29 (13.1)
Medical history: Dyslipidemia (e.g. hyperlipidemia) – n (%)	
Absent	169 (76.1)
Present	0
Unknown/not recorded	53 (23.9)
Medical history: Autoimmune disease – n (%)	
Absent	192 (86.5)
Present	0
Unknown/not recorded	30 (13.5)
Medical history: Cardiovascular disease – n (%)	

Factors	Safety analysis set N=222
Absent	186 (83.8)
Present	7 (3.2)
Unknown/not recorded	29 (13.1)
Height (cm)	
Number of patients	101
Mean (SD)	160.07 (9.794)
Median (minimum – maximum)	160.00 (140.6 - 187.0)
Weight (kg)	
Number of patients	101
Mean (SD)	64.33 (13.477)
Median (minimum – maximum)	63.90 (34.5 - 104.0)
BMI (kg/m^2)	
Number of patients	98
Mean (SD)	25.09 (4.103)
Median (minimum – maximum)	24.75 (16.4 - 37.5)
BMI category – n (%)	
< 25 kg/m^2	51 (23.0)
≥ 25 kg/m^2	47 (21.2)
Unknown/not recorded	124 (55.9)
HbA1c (%)	
Number of patients	152
Mean (SD)	7.50 (1.543)
Median (minimum – maximum)	7.10 (5.1 - 12.0)
HbA1c category – n (%)	
< 7%	67 (30.2)
≥ 7%	85 (38.3)
Unknown/not recorded	70 (31.5)
Smoking history – n (%)	

Factors	Safety analysis set N=222
Nonsmoker	75 (33.8)
Former smoker	19 (8.6)
Current smoker	16 (7.2)
Unknown/not recorded	112 (50.5)

The denominator for the proportion was the number of patients in the safety analysis set (N).

Demographics and disease characteristics for each treated eye (safety analysis set)

Factors	Safety analysis set N=222	
	Primary treated eye m=222	Secondary treated eye m=41
Classification of diabetic retinopathy – n (%)		
Nonproliferative diabetic retinopathy	118 (53.2)	19 (46.3)
Proliferative diabetic retinopathy	94 (42.3)	17 (41.5)
Unknown/not recorded	10 (4.5)	5 (12.2)
Concurrent (ongoing) glaucoma (POAG) – n (%)		
Absent	214 (96.4)	38 (92.7)
Present	8 (3.6)	1 (2.4)
Unknown/not recorded	0	2 (4.9)
Concurrent (ongoing) glaucoma (NTG) – n (%)		
Absent	217 (97.7)	39 (95.1)
Present	5 (2.3)	0
Unknown/not recorded	0	2 (4.9)
Concurrent (ongoing) ocular hypertension – n (%)		

Factors	Safety analysis set N=222	
	Primary treated eye m=222	Secondary treated eye m=41
Absent	207 (93.2)	36 (87.8)
Present	15 (6.8)	3 (7.3)
Unknown/not recorded	0	2 (4.9)
History of endophthalmitis (healed) – n (%)		
Absent	221 (99.5)	38 (92.7)
Present	1 (0.5)	1 (2.4)
Unknown/not recorded	0	2 (4.9)
History of intraocular inflammation (healed) – n (%)		
Absent	218 (98.2)	37 (90.2)
Present	4 (1.8)	2 (4.9)
Unknown/not recorded	0	2 (4.9)
History of retinal vasculitis (healed) – n (%)		
Absent	221 (99.5)	38 (92.7)
Present	1 (0.5)	1 (2.4)
Unknown/not recorded	0	2 (4.9)
History of retinal vascular occlusion (healed) – n (%)		
Absent	220 (99.1)	38 (92.7)
Present	2 (0.9)	1 (2.4)
Unknown/not recorded	0	2 (4.9)
Prior treatment with VEGF inhibitors* – n (%)		
Absent	118 (53.2)	27 (65.9)
Present	102 (45.9)	12 (29.3)
Unknown/not recorded	2 (0.9)	2 (4.9)
Prior treatment with VEGF inhibitors*: Lucentis/ranibizumab – n (%)		
Absent	201 (90.5)	34 (82.9)

Factors	Safety analysis set N=222 Primary treated eye m=222	 Secondary treated eye m=41
Present	19 (8.6)	5 (12.2)
Unknown/not recorded	2 (0.9)	2 (4.9)
Prior treatment with VEGF inhibitors*: Eylea/aflibercept – n (%)		
Absent	162 (73.0)	35 (85.4)
Present	58 (26.1)	4 (9.8)
Unknown/not recorded	2 (0.9)	2 (4.9)
Prior treatment with VEGF inhibitors*: Vabysmo/faricimab – n (%)		
Absent	195 (87.8)	36 (87.8)
Present	25 (11.3)	3 (7.3)
Unknown/not recorded	2 (0.9)	2 (4.9)
Prior treatment with VEGF inhibitors*: Other – n (%)		
Absent	220 (99.1)	39 (95.1)
Present	0	0
Unknown/not recorded	2 (0.9)	2 (4.9)
Number of days switched from other VEGF inhibitors* (days)		
Number of patients	101	11
Mean (SD)	78.9 (40.38)	106.0 (39.26)
Median (minimum – maximum)	67.0 (28 - 178)	112.0 (35 - 167)
Number of days switched from other VEGF inhibitors* (days) – n (%)**		
Number of patients	102	12
< 28 days	0	0
≥ 28 days	101 (99.0)	11 (91.7)
Unknown/not recorded	1 (1.0)	1 (8.3)
Reason for switch from other VEGF inhibitors* (days) – n (%)**		

Factors	Safety analysis set N=222 Primary treated eye m=222	Secondary treated eye m=41
Number of patients	102	12
Inadequate response	93 (91.2)	9 (75.0)
Safety issues	0	0
Dosing interval prolongation	8 (7.8)	2 (16.7)
Others	1 (1.0)	0
Unknown/not recorded	0	1 (8.3)
Prior treatment with steroids* – n (%)		
Absent	199 (89.6)	38 (92.7)
Present	18 (8.1)	1 (2.4)
Unknown/not recorded	5 (2.3)	2 (4.9)
Prior treatment with steroids*: Intravitreal injection – n (%)		
Absent	210 (94.6)	39 (95.1)
Present	7 (3.2)	0
Unknown/not recorded	5 (2.3)	2 (4.9)
Prior treatment with steroids*: sub-Tenon's injection – n (%)		
Absent	208 (93.7)	38 (92.7)
Present	9 (4.1)	1 (2.4)
Unknown/not recorded	5 (2.3)	2 (4.9)
Prior treatment with steroids*: Other – n (%)		
Absent	215 (96.8)	39 (95.1)
Present	2 (0.9)	0
Unknown/not recorded	5 (2.3)	2 (4.9)
History of macular photocoagulation* – n (%)		
Absent	200 (90.1)	38 (92.7)
Present	14 (6.3)	0

Factors	Safety analysis set N=222	
	Primary treated eye m=222	Secondary treated eye m=41
Unknown/not recorded	8 (3.6)	3 (7.3)
History of peripheral photocoagulation* – n (%)		
Absent	185 (83.3)	35 (85.4)
Present	25 (11.3)	3 (7.3)
Unknown/not recorded	12 (5.4)	3 (7.3)
History of panretinal photocoagulation (PRP)* − n (%)		
Absent	165 (74.3)	25 (61.0)
Present	50 (22.5)	15 (36.6)
Unknown/not recorded	7 (3.2)	1 (2.4)
History of vitrectomy* − n (%)		
Absent	209 (94.1)	39 (95.1)
Present	11 (5.0)	1 (2.4)
Unknown/not recorded	2 (0.9)	1 (2.4)

Unless otherwise recorded, the denominator for the proportion was the number of patients with the analysis eye (m).

* Prior medications were defined as medications administered during the period from 6 months before the start date of observation (start date of treatment in the primary treated eye) to the day before the start date of Beovu treatment in each eye, or medications collected as prior medications but used during Beovu treatment period.

** The denominator for the proportion was the number of patients with prior treatment with VEGF inhibitors.

Primary Outcome Result(s)

Refer to the safety Results section for primary outcome results.

Secondary Outcome Result(s)

VA worsening (safety analysis set)

Analyzed patients* N=198	Primary treated eye m=196 n (%)	(95% CI)	Secondary treated eye m=37 n (%)	(95% CI)
During the observation period				
≥ 50% decrease**	27 (13.8)	(9.3, 19.4)	2 (5.4)	(0.7, 18.2)
≥ 75% decrease**	8 (4.1)	(1.8, 7.9)	0	-
At last evaluation point				
≥ 50% decrease	12 (6.1)	(3.2, 10.5)	2 (5.4)	(0.7, 18.2)
≥ 75% decrease	2 (1.0)	(0.1, 3.6)	0	-

* Analyzed patient: among the patients in the safety analysis set, those who had decimal VA recorded at least once at baseline and during the observation period were included.

** Counted for any decrease in VA during the observation period.

95% CI was calculated using the Clopper-Pearson method.

The denominator for the proportion was the number of patients with the analysis eye (m).

Treatment status (safety analysis set)

	Safety analysis set N=222 Primary treated eye m=222	Secondary treated eye m=41
Duration of treatment (days)		
Number of patients	222	41
Mean (SD)	314.3 (100.02)	263.1 (97.65)
Median	365.0	288.0
Q1 - Q3	365.0 - 365.0	197.0 - 351.0
Minimum – maximum	2 - 365	36 - 365

	Safety analysis set N=222	
	Primary treated eye m=222	Secondary treated eye m=41
Duration category – n (%)		
< 3 months	3 (1.4)	3 (7.3)
3 to < 6 months	32 (14.4)	7 (17.1)
6 to < 9 months	11 (5.0)	6 (14.6)
9 to < 12 months	6 (2.7)	20 (48.8)
≥ 12 months	170 (76.6)	5 (12.2)
Number of doses (doses)		
Number of patients	222	41
Mean (SD)	3.5 (2.06)	3.2 (1.72)
Median	3.0	3.0
Q1 - Q3	2.0 - 5.0	2.0 - 4.0
Minimum – maximum	1 - 8	1 - 7
Category of number of doses – n (%)		
1 dose	52 (23.4)	8 (19.5)
2 doses	31 (14.0)	8 (19.5)
3 doses	38 (17.1)	9 (22.0)
4 doses	22 (9.9)	7 (17.1)
5 doses	30 (13.5)	3 (7.3)
6 doses	27 (12.2)	5 (12.2)
7 doses	19 (8.6)	1 (2.4)
8 doses	3 (1.4)	0
Induction phase (days)		
Number of patients	222	41
Mean (SD)	43.5 (59.20)	23.6 (31.80)
Median	1.0	1.0

	Safety analysis set N=222	
	Primary treated eye m=222	Secondary treated eye m=41
Q1 - Q3	1.0 - 85.0	0.0 - 43.0
Minimum – maximum	0 - 269	0 - 99
Number of doses in the induction phase (doses)		
Number of patients	222	41
Mean (SD)	1.8 (1.48)	1.3 (1.05)
Median	1.0	1.0
Q1 - Q3	1.0 - 3.0	0.0 - 2.0
Minimum – maximum	0 - 6	0 - 3
Category of number of doses in the induction phase – n (%)		
0 doses	42 (18.9)	11 (26.8)
1 dose	84 (37.8)	14 (34.1)
2 doses	21 (9.5)	9 (22.0)
3 doses	49 (22.1)	7 (17.1)
4 doses	9 (4.1)	0
5 doses	16 (7.2)	0
6 doses	1 (0.5)	0
Category of number of doses in the induction phase in patients with prior treatment with other VEGF inhibitors* – n (%)		
Number of patients	102	12
0 doses	31 (30.4)	4 (33.3)
1 dose	33 (32.4)	4 (33.3)
2 doses	8 (7.8)	2 (16.7)
3 doses	17 (16.7)	2 (16.7)
4 doses	7 (6.9)	0
5 doses	5 (4.9)	0

	Safety analysis set N=222 Primary treated eye m=222	Secondary treated eye m=41
6 doses	1 (1.0)	0
Category of number of doses in the induction phase in patients without prior treatment with other VEGF inhibitors* – n (%)		
Number of patients	118	27
0 doses	9 (7.6)	6 (22.2)
1 dose	51 (43.2)	10 (37.0)
2 doses	13 (11.0)	7 (25.9)
3 doses	32 (27.1)	4 (14.8)
4 doses	2 (1.7)	0
5 doses	11 (9.3)	0
Maintenance phase (days)		
Number of patients	222	41
Mean (SD)	270.7 (103.90)	239.5 (99.88)
Median	299.0	280.0
Q1 - Q3	196.0 - 364.0	196.0 - 315.0
Minimum – maximum	1 - 365	29 - 364
Number of doses in the maintenance phase (doses)		
Number of patients	222	41
Mean (SD)	1.8 (1.73)	1.9 (1.51)
Median	1.0	1.0
Q1 - Q3	0.0 - 3.0	1.0 - 3.0
Minimum – maximum	0 - 6	0 - 5
Category of number of doses in the maintenance phase – n (%)		
0 doses	75 (33.8)	8 (19.5)
1 dose	41 (18.5)	13 (31.7)

	Safety analysis set N=222	
	Primary treated eye m=222	Secondary treated eye m=41
2 doses	34 (15.3)	4 (9.8)
3 doses	33 (14.9)	9 (22.0)
4 doses	20 (9.0)	5 (12.2)
5 doses	12 (5.4)	2 (4.9)
6 doses	7 (3.2)	0
Dosing interval – n (%)		
Reduction** present	54 (24.3)	--
Reduction** absent	168 (75.7)	--

* Prior medications were defined as medications administered during the period from 6 months before the start date of observation (start date of treatment in the primary treated eye) to the day before the start date of Beovu treatment in each eye, or medications collected as prior medications but used during Beovu treatment period.

** Dosing interval reduction was defined as cases in which the dosing interval in the primary treated eye was either "< 42 days in the induction phase" or "< 56 days in the maintenance phase," or both.

Unless otherwise recorded, the denominator for the proportion was the number of patients with the analysis eye (m).

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

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All-Cause Mortality

List of adverse events leading to death (safety analysis set)

Age/ sex	Event term (verbatim term/PT)	Number of days to onset (days)	Number of days to death (days)	Outcome	Causal relationship to Beovu	Causal relationship to administration procedures
88/male	Death/ Death	102	1	Death	0	0

Serious Adverse Events

Incidence of serious adverse events in the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 Primary treated eye m=222 n (%)	 Secondary treated eye m=41 n (%)
Total	5 (2.3)	2 (4.9)
Eye disorders	4 (1.8)	1 (2.4)
Vitreous haemorrhage	3 (1.4)	0
Vitritis	1 (0.5)	0
Diabetic retinal oedema	0	1 (2.4)
Investigations	0	1 (2.4)
Intraocular pressure increased	0	1 (2.4)
Injury, poisoning and procedural complications	1 (0.5)	0
Cataract traumatic	1 (0.5)	0

Multiple PTs in the same SOC in the same treated eye were counted as 1 patient.

The same PT occurring more than once in the same treated eye was counted as 1 patient.

SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence in primary treated eye > order of the PT code and 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 analysis eye (m).
MedDRA/J version 27.0

Incidence of serious systemic (non-ocular) adverse events (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 n (%)
Total	3 (1.4)
Nervous system disorders	1 (0.5)
Cerebral infarction	1 (0.5)
Renal and urinary disorders	1 (0.5)
Renal impairment	1 (0.5)
General disorders and administration site conditions	1 (0.5)
Death	1 (0.5)

Multiple PTs in the same SOC in the same patient were counted as 1 patient.
The same PT occurring more than once the same patient was counted as 1 patient.
SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence > order of the PT code.
The denominator for the proportion was the number of patients in the safety analysis set (N).
MedDRA/J version 27.0

Incidence of serious adverse reactions in the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 Primary treated eye m=222 n (%)	 Secondary treated eye m=41 n (%)
Total	2 (0.9)	1 (2.4)
Eye disorders	1 (0.5)	0
Vitritis	1 (0.5)	0
Investigations	0	1 (2.4)

SOC PT	Safety analysis set N=222 Primary treated eye m=222 n (%)	 Secondary treated eye m=41 n (%)
Intraocular pressure increased	0	1 (2.4)
Injury, poisoning and procedural complications	1 (0.5)	0
Cataract traumatic	1 (0.5)	0

Multiple PTs in the same SOC in the same treated eye were counted as 1 patient.
The same PT occurring more than once in the same treated eye was counted as 1 patient.
SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence in primary treated eye > order of the PT code and 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 analysis eye (m).
MedDRA/J version 27.0

Incidence of serious systemic (non-ocular) adverse reactions (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 n (%)
Total	1 (0.5)
Renal and urinary disorders	1 (0.5)
Renal impairment	1 (0.5)

Multiple PTs in the same SOC in the same patient were counted as 1 patient.
The same PT occurring more than once the same patient was counted as 1 patient.
SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence > order of the PT code.
The denominator for the proportion was the number of patients in the safety analysis set (N).
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Other Adverse Events

Incidence of adverse events in the treated eye (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 Primary treated eye m=222 n (%)	 Secondary treated eye m=41 n (%)
Total	14 (6.3)	4 (9.8)
Eye disorders	13 (5.9)	3 (7.3)
Vitreous haemorrhage	3 (1.4)	1 (2.4)
Vitritis	3 (1.4)	0
Ocular hypertension	2 (0.9)	0
Eye inflammation	1 (0.5)	0
Iritis	1 (0.5)	0
Retinal ischaemia	1 (0.5)	0
Retinal vasculitis	1 (0.5)	0
Uveitis	1 (0.5)	0
Vitreous floaters	1 (0.5)	0
Anterior chamber inflammation	1 (0.5)	0
Retinal aneurysm rupture	1 (0.5)	0
Diabetic retinal oedema	0	1 (2.4)
Vitreous opacities	0	1 (2.4)
Investigations	0	1 (2.4)
Intraocular pressure increased	0	1 (2.4)
Injury, poisoning and procedural complications	2 (0.9)	0
Cataract traumatic	1 (0.5)	0
Persistent corneal epithelial defect	1 (0.5)	0

Multiple PTs in the same SOC in the same treated eye were counted as 1 patient.
The same PT occurring more than once in the same treated eye was counted as 1 patient.

SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence in primary treated eye > order of the PT code and 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 analysis eye (m).
MedDRA/J version 27.0

Incidence of systemic (non-ocular) adverse events (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 n (%)
Total	5 (2.3)
Nervous system disorders	1 (0.5)
Cerebral infarction	1 (0.5)
Cardiac disorders	1 (0.5)
Arrhythmia	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (0.5)
Cough	1 (0.5)
Renal and urinary disorders	2 (0.9)
Incontinence	1 (0.5)
Renal impairment	1 (0.5)
General disorders and administration site conditions	2 (0.9)
Death	1 (0.5)
Malaise	1 (0.5)

Multiple PTs in the same SOC in the same patient were counted as 1 patient.
The same PT occurring more than once the same patient was counted as 1 patient.
SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence > order of the PT code.
The denominator for the proportion was the number of patients in the safety analysis set (N).
MedDRA/J version 27.0

Incidence of adverse reactions in the treated eye (by SOC and PT) (safety analysis set)

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SOC PT	Safety analysis set N=222 Primary treated eye m=222 n (%)	 Secondary treated eye m=41 n (%)
Total	8 (3.6)	2 (4.9)
Eye disorders	7 (3.2)	1 (2.4)
Vitritis	3 (1.4)	0
Eye inflammation	1 (0.5)	0
Iritis	1 (0.5)	0
Retinal vasculitis	1 (0.5)	0
Uveitis	1 (0.5)	0
Vitreous floaters	1 (0.5)	0
Anterior chamber inflammation	1 (0.5)	0
Vitreous opacities	0	1 (2.4)
Investigations	0	1 (2.4)
Intraocular pressure increased	0	1 (2.4)
Injury, poisoning and procedural complications	1 (0.5)	0
Cataract traumatic	1 (0.5)	0

Multiple PTs in the same SOC in the same treated eye were counted as 1 patient.

The same PT occurring more than once in the same treated eye was counted as 1 patient.

SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence in primary treated eye > order of the PT code and 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 analysis eye (m).

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Incidence of systemic (non-ocular) adverse reactions (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=222 n (%)
Total	3 (1.4)
Cardiac disorders	1 (0.5)
Arrhythmia	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (0.5)
Cough	1 (0.5)
Renal and urinary disorders	2 (0.9)
Incontinence	1 (0.5)
Renal impairment	1 (0.5)
General disorders and administration site conditions	1 (0.5)
Malaise	1 (0.5)

Multiple PTs in the same SOC in the same patient were counted as 1 patient.
The same PT occurring more than once the same patient was counted as 1 patient.
SOC is shown in the internationally agreed order, PT is shown in the descending order of incidence > order of the PT code.
The denominator for the proportion was the number of patients in the safety analysis set (N).
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Incidence of safety specifications (adverse events and serious adverse events) (safety specifications, by PT) (safety analysis set)

Safety specifications PT	Safety analysis set N=222 Adverse events Primary treated eye m=222 n (%)	Secondary treated eye m=41 n (%)	Systemic (non-ocular) m=222 n (%)	Serious adverse events Primary treated eye m=222 n (%)	Secondary treated eye m=41 n (%)	Systemic (non-ocular) m=222 n (%)
Total	7 (3.2)	2 (4.9)	1 (0.5)	1 (0.5)	1 (2.4)	1 (0.5)
Intraocular inflammation	6 (2.7)	1 (2.4)	--	1 (0.5)	0	--

Safety specifications PT	Safety analysis set N=222 Adverse events Primary treated eye m=222 n (%)	Secondary treated eye m=41 n (%)	Systemic (non-ocular) m=222 n (%)	Serious adverse events Primary treated eye m=222 n (%)	Secondary treated eye m=41 n (%)	Systemic (non-ocular) m=222 n (%)
Vitritis	3 (1.4)	0	--	1 (0.5)	0	--
Eye inflammation	1 (0.5)	0	--	0	0	--
Iritis	1 (0.5)	0	--	0	0	--
Retinal vasculitis	1 (0.5)	0	--	0	0	--
Uveitis	1 (0.5)	0	--	0	0	--
Anterior chamber inflammation	1 (0.5)	0	--	0	0	--
Vitreous opacities	0	1 (2.4)	--	0	0	--
Increased intraocular pressure	0	1 (2.4)	--	0	1 (2.4)	--
Intraocular pressure increased	0	1 (2.4)	--	0	1 (2.4)	--
Retinal arterial embolic events	1 (0.5)	0	--	0	0	--
Retinal ischaemia	1 (0.5)	0	--	0	0	--
Retinal vasculitis and retinal vascular occlusion	2 (0.9)	0	--	0	0	--
Retinal ischaemia	1 (0.5)	0	--	0	0	--
Retinal vasculitis	1 (0.5)	0	--	0	0	--
Non-ocular arterial thromboembolic events	--	--	1 (0.5)	--	--	1 (0.5)
Cerebral infarction	--	--	1 (0.5)	--	--	1 (0.5)

Safety specifications: For ocular events, multiple PTs in the same safety specification in the same treated eye were counted as 1 patient.

For systemic events, multiple PTs in the same specification in the same patient were counted as 1 patient.

PT: For ocular events, the same PT occurring more than once in the same treated eye was counted as 1 patient.

For systemic events, the same PT occurring more than once in the same patient was counted as 1 patient.

PT for ocular events is shown in the descending order of incidence in the row of adverse events in the primary treated eye > order of the PT code and descending order of incidence in the row of adverse events in the secondary treated eye > order of the PT code.

PT for systemic events is shown in descending order of incidence in the row of adverse events > order of the PT code.

The denominator of the proportion was the number of patients with the analysis eye for ocular events and the number of patients in the safety analysis set (m) for systemic events.
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Incidence of safety specifications (adverse reactions and serious adverse reactions) (safety specifications, by PT) (safety analysis set)

	Safety analysis set N=222					
	Adverse reactions			Serious adverse reactions		
Safety specifications PT	Primary treated eye m=222 n (%)	Secondary treated eye m=41 n (%)	Systemic (non-ocular) m=222 n (%)	Primary treated eye m=222 n (%)	Secondary treated eye m=41 n (%)	Systemic (non-ocular) m=222 n (%)
Total	6 (2.7)	2 (4.9)	0	1 (0.5)	1 (2.4)	0
Intraocular inflammation	6 (2.7)	1 (2.4)	--	1 (0.5)	0	--
Vitritis	3 (1.4)	0	--	1 (0.5)	0	--
Eye inflammation	1 (0.5)	0	--	0	0	--
Iritis	1 (0.5)	0	--	0	0	--
Retinal vasculitis	1 (0.5)	0	--	0	0	--
Uveitis	1 (0.5)	0	--	0	0	--
Anterior chamber inflammation	1 (0.5)	0	--	0	0	--
Vitreous opacities	0	1 (2.4)	--	0	0	--
Increased intraocular pressure	0	1 (2.4)	--	0	1 (2.4)	--
Intraocular pressure increased	0	1 (2.4)	--	0	1 (2.4)	--
Retinal vasculitis and retinal vascular occlusion	1 (0.5)	0	--	0	0	--
Retinal vasculitis	1 (0.5)	0	--	0	0	--

Safety specifications: For ocular events, multiple PTs in the same safety specification in the same treated eye were counted as 1 patient.
For systemic events, multiple PTs in the same specification in the same patient were counted as 1 patient.
PT: For ocular events, the same PT occurring more than once in the same treated eye was counted as 1 patient.
For systemic events, the same PT occurring more than once in the same patient was counted as 1 patient.

PT for ocular events is shown in the descending order of incidence in the row of adverse reactions in the primary treated eye > order of the PT code and descending order of incidence in the row of adverse reactions in the secondary treated eye > order of the PT code.
PT for systemic events is shown in descending order of incidence in the row of adverse reactions > order of the PT code.
The denominator of the proportion was the number of patients with the analysis eye for ocular events and the number of patients in the safety analysis set (m) for systemic events.
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Other Relevant Findings

Not applicable

Conclusion:

Based on the safety results of this study, the adverse events and adverse reactions reported were mostly known events, and there were no noteworthy trends or concerns regarding the types, seriousness, and outcomes of these events. Based on the above, it was considered unnecessary to take additional measures based on the results of this study.

Date of Clinical Trial Report

10 March 2025