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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab and Ranibizumab.

Trial Indication(s)

Neovascular Age-Related Macular Degeneration

Protocol Number

CRTH258A2402

Protocol Title

A non-interventional study to assess the influence of automated optical coherence tomography (OCT) image enrichment with segmentation information on disease activity assessment in patients treated with licensed anti- VEGF injections

Clinical Trial Phase

Phase IV

Phase of Drug Development

Approval

Study Start/End Dates

Study Start Date: February 23, 2021 (Actual)

Primary Completion Date: June 28, 2023 (Actual)
Study Completion Date: June 28, 2023 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was an observational, multicenter, multinational, open-label, study designed primarily to investigate the influence of automated optical coherence tomography (OCT) image enrichment with segmentation information on disease activity assessment in neovascular age-related macular degeneration (nAMD) patients treated with licensed anti- vascular endothelial growth factor (VEGFs). The study comprised a prospective data collection phase and a retrospective analysis of OCT images phase. The prospective observation period per patient was up to 12 months.

The study included 444 patients in the full analysis set (naïve patients and patients who have been pre-treated with licensed anti-VEGFs not more than 3 years) being treated for nAMD with brolucizumab, ranibizumab, or aflibercept according to the respective drug label.

Centers

17 centers in 5 countries: Germany(6), Canada(3), Spain(4), Ireland(2), Italy(2)

Objectives:

Primary objective:

- To assess the influence of automated optical coherence tomography (OCT) image enrichment with segmentation information on disease activity assessment in patients treated with licensed anti- vascular endothelial growth factor (VEGF) injections for neovascular age-related macular degeneration (nAMD).

Secondary objectives:

- To assess if Discovery® was accepted by physicians and could optimize the ophthalmic clinical workflow.

- To assess the anatomical and functional results of brolucizumab and safety of brolucizumab and ranibizumab for treating nAMD in the real-world clinical setting.

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

Brolucizumab, Ranibizumab, or Aflibercept according to the respective drug label.

Statistical Methods

Descriptive statistics were tabulated for the demographic and clinical characteristics and outcome variables. To assess the influence of automated OCT image enrichment with segmentation information on disease activity assessment, a generalized linear mixed model (GLMM) was employed. Additionally, the degree of agreement in classification of disease activity across reviewers (with and without segmentation, separately) was assessed by Krippendorff's alpha. A bootstrap 95% confidence interval for alpha was reported.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Diagnosis of nAMD
- Male and Female patients with ≥18 years of age at index
- Receipt of at least one injection of brolucizumab, ranibizumab or aflibercept during the recruitment period
- Signed written informed consent
- Patients for whom a therapy with brolucizumab, ranibizumab or aflibercept is medically indicated according to the respective label
- Intraretinal and/or subretinal fluid affecting the central subfield of the study eye at screening

Exclusion Criteria:

-Patients treated for any other retinal disease than nAMD within 6 months prior to the index date (e.g. patients treated for retinal vein occlusion, diabetic macular oedema, myopic CNV, and have diagnoses of diabetes-related macular degeneration)

- Central subfield of the study eye affected by fibrosis or geographic atrophy or total area of fibrosis >50% of the total lesion in the study eye at screening
- Any active intraocular or periocular infection or active intraocular inflammation in either eye at index date
- Patients who have been on anti-VEGF treatment for longer than 3 years (before index date)
- Patients who have any contraindication and are not eligible for treatment with the chosen anti-VEGF treatment as according to the respective label.
- Any medical or psychological condition, in the treating physician's opinion, which may hinder the patient from participating in this study for the expected 12 months
- Patients participating, in parallel, in an interventional clinical trial
- Patients participating, in parallel, in any other Novartis sponsored NIS generating primary data for an anti-VEGF drug

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Participant Flow Table

Patient disposition and analysis sets

All patients	Total (N=476) n (%)
Number of patients	
Enrolled (i.e. baseline visit completed)	476 (100.0)
Included into FAS[a]	444 (93.3)
Included into FAS RR[b]	380 (79.8)
Included into SAF[c]	207 (43.5)
Number of enriched images	**380 (100.0)**
≤ 4 reviews	31 (8.2)
≤ 6 reviews	76 (20.0)
≤ 8 reviews	248 (65.3)
> 8 reviews	132 (34.7)
Number of non-enriched images	**380 (100.0)**
≤ 4 reviews	14 (3.7)
≤ 6 reviews	81 (21.3)
≤ 8 reviews	259 (68.2)
> 8 reviews	121 (31.8)

Abbreviations: FAS = Full Analysis Set, FAS RR = Full Analysis Set Retrospective Review, SAF = Safety Analysis Set

[a] 32 patients were excluded from the FAS because no anti-VEGF injection in the study eye was documented.

[b] 96 patients were excluded from the FAS RR because less than 2 reviews per image (enriched and non-enriched OCT) existed.

[c] All patients who were included in Phase 1 and are treated with brolucizumab or ranibizumab.

Study discontinuation

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All patients	Total (N=476) n (%)
Number of patients who discontinued treatment permanently and prematurely	20 (4.2)
Primary reason for discontinuation:	
Adverse event	1 (5.0)
Death	-
Technical issues	1 (5.0)
Nonappearance of patient for 6 months	1 (5.0)
Withdrawal of informed consent	1 (5.0)
Pregnancy	-
Anti-VEGF treatment off-label	7 (35.0)
Reason missing	9 (45.0)

Abbreviations: VEGF = Vascular Endothelial Growth Factor

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Baseline Characteristics

	FAS (N=444)	FAS RR (N=380)
Sex, n (%)		
Male	280 (63.1)	242 (63.7)
Female	164 (36.9)	138 (36.3)
Age at baseline (years)		
n	444	380
Mean ± SD	79 ± 8	79 ± 8
Median (range)	80 (56 to 99)	80 (56 to 99)
Smoker, n (%)		
Yes	40 (9.0)	36 (9.5)
No	298 (67.1)	256 (67.4)
Unknown	106 (23.9)	88 (23.2)
Race, n (%)		
American Indian or Alaska Native	5 (1.1)	5 (1.3)
Asian	6 (1.4)	5 (1.3)
White	433 (97.5)	370 (97.4)

Abbreviations: FAS = Full Analysis Set, FAS RR = Full Analysis Set Retrospective Review, SD = Standard Deviation

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Primary Outcome Result(s)

Odds ratio of Disease Activity Assessment (DAA): influence of automated OCT image enrichment

FAS RR Number of images = 380				
Estimates for DAA = yes		Enriched versus non-enriched OCT image		
Enriched OCT	Non-enriched OCT	Odds ratio	[95% CI]	p-value
0.759	0.772	1.078	[0.95; 1.22]	0.229

Abbreviations: CI = Confidence Interval, DAA = Disease Activity Assessment, FAS RR = Full Analysis Set Retrospective Review

Odds ratio and 95% CI obtained from a generalized linear mixed model (GLMM) that includes fixed effects for enrichment status and a random effect for reviewer.

Degree of agreement in classification of disease activity with and with-out OCT image enrichment, Krippendorff's alpha

FAS RR		
Reliability of reviewers ratings[a]	Enriched OCT image	Non-enriched OCT image
Number of images[b]	380	380
Number of raters	36	36
Krippendorff's alpha	0.416	0.402
95%-CI	[0.377; 0.456]	[0.359; 0.445]

Abbreviations: : CI = Confidence Interval, FAS RR = Full Analysis Set Retrospective Review

[a] Per patient one image is chosen for retrospective OCT image examination.

[b] Confidence intervals are calculated with Bootstrapping.

Krippendorff's alpha was calculated in R studio Version 4.2.3. Range from 0 to 1, where 0 means perfect disagreement and 1 means perfect agreement.

Secondary Outcome Result(s)

Difference in time needed for DAA between reviews with and without enrichment:

A secondary objective was to assess the influence of OCT enrichment on the speed of DAA. Therefore, the difference in time to DAA (time between begin of OCT viewing and result sub-mission) between cases reviewed with and without use of segmentation information was calculated.

FAS RR
Number of images = 380

	Enriched OCT	Non-enriched OCT	Comparison[b]: Enriched versus non-enriched OCT
DAA duration[a] (minutes)			**Mean difference [95% CI]:** 0.11 [0.04; 0.19] **p-value:** 0.003
n	380	380	
Mean ± SD	1.5 ± 0.6	1.4 ± 0.6	
Range	0.6 to 4.2	0.5 to 4.4	

Abbreviations: : CI = Confidence Interval, DAA = Disease Activity Assessment, FAS RR = Full Analysis Set Retrospective Review, OCT = Optical Coherence Tomography, SD = Standard deviation

[a] DAA duration was the time between begin of OCT viewing and result submission. Outliers over 15 minutes were excluded.

[b] The between-group difference was analysed by a paired t-test.

Sample statistics were calculated based on the mean values of assessments per image.

Difference in confidence in DAA between reviews with and without enrichment

A further secondary objective was to assess the influence of OCT enrichment on the confidence in DAA as rated by the physicians. Here the difference in confidence in DAA between cases reviewed with and without enrichment (rating of 1-10 per case, whereby a rating of 10 meant maximal confidence) was calculated.

FAS RR Number of images = 380			
	Enriched OCT	**Non-enriched OCT**	**Comparison[b]: Enriched versus non-enriched OCT**
Confidence[a]			**Mean difference [95% CI]:** 0.16 [0.08; 0.23] **p-value:** <0.001
n	380	380	
Mean ± SD	8.5 ± 0.8	8.3 ± 1.0	
Range	6.0 to 10.0	5.2 to 10.0	

Abbreviations: : CI = Confidence Interval, DAA = Disease Activity Assessment, FAS RR = Full Analysis Set Retrospective Review, OCT = Optical Coherence Tomography, SD = Standard deviation

[a] Confidence was rated on a scale from 1 to 10. 10 means maximal confidence.

[b] The between-group difference was analysed by a paired t-test.

Sample statistics were calculated based on the mean values of assessments per image.

Subjective assessment of system correctness

Furthermore, investigators should assess the correctness of the system on a scale from 0 to 10 (10 corresponds to maximum correctness) if segmentation algorithm was used.

FAS RR	
	Enriched OCT
System correctness[a]	
n (number of assessments)	2693
Mean ± SD	8.0 ± 1.7
Range	1.0 to 10.0

Abbreviations: : FAS RR = Full Analysis Set Retrospective Review, OCT = Optical Coherence Tomography, SD = Standard deviation

[a] System correctness was assessed by physicians if the segmentation algorithm was used (enriched OCT).

System correctness was rated on a scale from 1 to 10. 10 means maximal correctness.

Acceptance of Discovery® by physicians and whether it can optimize the ophthalmic clinical workflow:

Additionally, the physicians received a questionnaire with the goal to address the secondary study objective: assessment of the Discovery® platform regarding acceptance and usability to optimize the clinical workflow.

Questionnaire on user experience of Discovery® platform: Participation

Questionnaire	Total n (%)
Number of submitted questionnaires (overall)	32 (100.0)
Participation in Phase 1 only	6 (18.8)
Participation in Phase 2 only	11 (34.4)
Participation in Phase 1 and Phase 2	15 (46.9)

Item 6 of the questionnaire for physicians.

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Questionnaire on user experience of Discovery® platform: General information

Questionnaire	Total (N=32) n (%)
How long have you been practicing as retina specialist?	
I am not a retina specialist	4 (12.5)
0-4 years	5 (15.6)
5-9 years	11 (34.4)
10-19 years	8 (25.0)
20-30 years	2 (6.3)
> 30 years	2 (6.3)
Proportion of total time spent for reviewing OCT images?	
0-10%	1 (3.1)
11-20%	6 (18.8)
21-30%	3 (9.4)
31-40%	4 (12.5)
41-50%	3 (9.4)
51-60%	4 (12.5)
61-70%	4 (12.5)
71-80%	4 (12.5)
81-90%	1 (3.1)
91-100%	2 (6.3)
Time per image review without the support of AI? (minutes)	
< 1 min	10 (31.3)
1-5 min	17 (53.1)
5-10 min	4 (12.5)
Missing values	1 (3.1)

Abbreviations: AI = Artificial Intelligence, OCT = Optical Coherence Tomography
Item 2,3, and 4 of the questionnaire for physicians.

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Questionnaire on user experience of Discovery® platform: Usability of Discovery® Platform

Questionnaire	Total (N=32) n (%)
How well can Discovery® be integrated into the clinical workflow?[a]	
n missing	-
Mean ± SD	6.9 ± 2.2
Median (Range)	7.5 (2.0 to 10.0)
Does Discovery® provide a better overview on patient data compared to your currently used tool?	
Yes	6 (18.8)
No	4 (12.5)
Somewhat	11 (34.4)
Missing values	11 (34.4)
What features of Discovery did you find useful?[b]	
Data uploader	5 (15.6)
Automatic data storage	10 (31.3)
Automatic secured data sharing	9 (28.1)
eCRF data management	11 (34.4)
I did not find any features useful	4 (12.5)
Missing values	11 (34.4)
Is cloud based patient data access and automatic secured data sharing useful in your clinical routine	
Yes	11 (34.4)
No	7 (21.9)
Somewhat	2 (6.3)
I do not know/cannot assess	1 (3.1)
Missing values	11 (34.4)
Is the upload/download speed of OCT images to Discovery® fast enough?	
Yes	13 (40.6)
No	2 (6.3)
Somewhat	2 (6.3)
I do not know/cannot assess	4 (12.5)
Missing values	11 (34.4)

Abbreviations: OCT = Optical Coherence Tomography, SD = Standard Deviation
[a] 0 = not well, 10 = extremely well
[b] Multiple answers were possible.
Item 5, 7, 8, and 9 of the questionnaire only answered by physicians who participated in Phase 1.

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Questionnaire on user experience of Discovery® platform: AI insights with Discovery® (I)

Questionnaire	Total (N=32) n (%)
Did you find AI insight view useful?	
Yes	20 (62.5)
No	6 (18.8)
Missing values	6 (18.8)
How useful did you find automatic segmentation?[a]	
0	1 (3.1)
1	1 (3.1)
2	2 (6.3)
5	2 (6.3)
6	1 (3.1)
7	6 (18.8)
8	9 (28.1)
9	3 (9.4)
10	1 (3.1)
Missing values	6 (18.8)
Usefulness of the automatic segmentation?[b]	
It saves time	17 (53.1)
It provides additional information	11 (34.4)
It optimizes clinical decision making	12 (37.5)
I did not find useful	3 (9.4)
Missing value	6 (18.8)

Abbreviations: AI = Artificial Intelligence
[a] 0 = not useful at all; 10= extremely useful
[b] Multiple answers were possible.
Item 11, 13, and 14 of the questionnaire were only answered by physicians who participated in Phase 2.

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Questionnaire on user experience of Discovery® platform: AI insights with Discovery® (II)

Questionnaire	N= 32 n (%)			
Ranking of AI insights view[a]	**1**	**2**	**3**	**4**
Segmentation OCT	15 (46.9)	4 (12.5)	1 (3.1)	-
Segmentation OCT (enface)	2 (6.3)	6 (18.8)	8 (25.0)	4 (12.5)
Biomarkers OCT	3 (9.4)	9 (28.1)	5 (15.6)	3 (9.4)
Biomarkers OCT (enface)	-	1 (3.1)	6 (18.8)	13 (40.6)
Missing values	12 (37.5)	12 (37.5)	12 (37.5)	12 (37.5)

Abbreviations: AI = Artificial Intelligence, OCT = Optical Coherence Tomography

[a] 1 = more useful to 4 = less useful

Item 12 of the questionnaire for physicians.

Percentage (%) of patients absent of Subretinal Fluid, Intraretinal Fluid and Pigment Epithelium Detachment by visit for patients treated with brolucizumab (study eye)

A further secondary objective was to evaluate anatomical and functional results of broluci-zumab treatment during Phase 1 of this study.

FAS Fluid resolution[a]	Baseline (N=30) n (%)	Month 3 (N=27) n (%)	Month 6 (N=25) n (%)	Month 9 (N=22) n (%)	Month 12 (N=12) n (%)
IRF					
Absent	14 (46.7)	12 (44.4)	12 (48.0)	6 (27.3)	3 (25.0)
Present	10 (33.3)	6 (22.2)	4 (16.0)	4 (18.2)	2 (16.7)
Unknown	-	2 (7.4)	2 (8.0)	2 (9.1)	1 (8.3)
Missing	6 (20.0)	7 (25.9)	7 (28.0)	10 (45.5)	6 (50.0)
SRF					
Absent	5 (16.7)	4 (14.8)	2 (8.0)	2 (9.1)	-
Present	19 (63.3)	16 (59.3)	15 (60.0)	12 (54.5)	7 (58.3)
Unknown	-	-	-	-	-
Missing	6 (20.0)	7 (25.9)	8 (32.0)	8 (36.4)	5 (41.7)
SRF and IRF					
Absent	-	2 (7.4)	1 (4.0)	2 (9.1)	-
Present	5 (16.7)	2 (7.4)	2 (8.0)	4 (18.2)	2 (16.7)

FAS Fluid resolution[a]	Baseline (N=30) n (%)	Month 3 (N=27) n (%)	Month 6 (N=25) n (%)	Month 9 (N=22) n (%)	Month 12 (N=12) n (%)
Unknown	-	-	-	-	-
No agreement	19 (63.3)	14 (51.9)	14 (56.0)	6 (27.3)	4 (33.3)
Missing	6 (20.0)	9 (33.3)	8 (32.0)	10 (45.5)	6 (50.0)
PED					
Absent	2 (6.7)	2 (7.4)	-	-	-
Present	19 (63.3)	18 (66.7)	16 (64.0)	12 (54.5)	6 (50.0)
Unknown	2 (6.7)	1 (3.7)	1 (4.0)	2 (9.1)	1 (8.3)
Missing	7 (23.3)	6 (22.2)	8 (32.0)	8 (36.4)	5 (41.7)

Abbreviations: FAS = Full Analysis Set, IRF = Intraretinal Fluid, PED = Pigment Epithelial Detachment, SRF = Subretinal Fluid
[a] Only the subgroup of patients receiving brolucizumab was analysed.

The “time to absence of IRF/SRF/PED analysis during the first year of treatment” using Kaplan-Meier method for patients with these conditions at baseline (n=30) compared to patients with this condition at month 12 (n=12), was not done due to small sample size

Central Subfield Thickness - Course and change from baseline up to month 12 (study eye)

FAS		Total (N=30)	
CST[a] (µm)	n	Mean ± SD	Median (range)
Course			
Baseline	17	321.4 ± 104.3	321.0 (169.0, 549.0)
Month 3	12	293.0 ± 110.0	256.0 (215.0, 613.0)
Month 6	12	326.3 ± 73.6	313.5 (165.0, 423.0)
Month 9	10	297.8 ± 69.6	289.5 (213.0, 445.0)
Month 12	5	293.8 ± 45.5	275.0 (254.0, 368.0)
Difference to baseline			
Month 3	12	-35.9 ± 70.4	-17.5 (-171.0, 64.0)
Month 6	12	-19.5 ± 84.9	-11.5 (-166.0, 188.0)
Month 9	10	-33.6 ± 54.4	-29.0 (-166.0, 38.0)
Month 12	5	-69.2 ± 69.8	-71.0 (-181.0, -5.0)

Abbreviations: CST = Central Subfield Thickness, FAS = Full Analysis Set, SD = Standard Deviation

[a] Only the subgroup of patients receiving brolucizumab was analysed

Please note that the calculations of the association between CST variability during the study and BCVA change from baseline to month 12 and the association between CST variability during the study and the number of injections during the first year of treatment with brolucizumab were not done due to small sample size (only 5 CST values at month 12 available).

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Best-corrected visual acuity – Course and change from baseline up to month 12 (study eye)

FAS		Total (N=30)	
ETDRS[a]	n	Mean ± SD	Median (range)
Course			
Baseline	28	66.2 ± 15.0	69.9 (19.9, 85.0)
Month 3	26	65.2 ± 14.8	65.1 (19.9, 85.0)
Month 6	23	68.0 ± 10.3	69.9 (35.0, 85.0)
Month 9	21	66.7 ± 11.7	65.1 (35.0, 85.0)
Month 12	12	67.2 ± 17.2	76.2 (35.0, 85.0)
Difference to baseline			
Month 3	24	0.6 ± 6.9	0.0 (-10.2, 14.7)
Month 6	22	0.6 ± 8.9	0.0 (-15.1, 15.1)
Month 9	21	-0.9 ± 9.3	0.0 (-19.0, 15.1)
Month 12	12	-0.9 ± 11.2	0.0 (-25.1, 15.1)

Abbreviations: BCVA = Best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS = Full Analysis Set, SD = Standard Deviation

[a] Only the subgroup of patients receiving brolucizumab was analysed

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Overview of AEs in nAMD patients treated with brolucizumab or ranibizumab:

SAF (N=207)	Non-ocular	Study eye	Fellow eye	Any AE
Number of patients with at least one AE, n (%)	**21 (10.1)**	**28 (13.5)**	**18 (8.7)**	**46 (22.2)**
nsAE	13 (6.3)	15 (7.2)	12 (5.8)	28 (13.5)
nsADR	-	3 (1.4)	3 (1.4)	3 (1.4)
nsAEnr	13 (6.3)	15 (7.2)	11 (5.3)	28 (13.5)
SAE	11 (5.3)	16 (7.7)	12 (5.8)	30 (14.5)
SADR	-	6 (2.9)	2 (1.0)	6 (2.9)
SAEnr	11 (5.3)	11 (5.3)	10 (4.8)	27 (13.0)
Number of events (overall)	**31**	**63**	**36**	**114**
nsAE	17	33	22	60
nsADR	0	3	3	3
nsAEnr	17	30	19	57
SAE	14	30	14	54
SADR	0	10	2	10
SAEnr	14	20	12	44

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, nr = not related, ns = non-serious, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SAF = Safety Analysis Set

Seriousness assessed with 'yes' by physicians or pharmacovigilance.

Causality of ADRs referred to treatment with brolucizumab or ranibizumab.

AEs without information on relation or seriousness were considered as related or serious.

Safety Results

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Table 10-27: Adverse events in the context of the study eye by SOC and PT (in nAMD patients treated with brolucizumab or ranibizumab)

SAF (N=207)	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
SOC (MedDRA v24.0 to v26.0) **PT**							
Number of patients with at least one AE, n (%)	**15 (7.2)**	**3 (1.4)**	**15 (7.2)**	**11 (5.3)**	**6 (2.9)**	**16 (7.7)**	**28 (13.5)**
Eye disorder	**13 (6.3)**	**-**	**13 (6.3)**	**11 (5.3)**	**6 (2.9)**	**16 (7.7)**	**26 (12.6)**
Eye pain	8 (3.9)	-	8 (3.9)	-	-	-	8 (3.9)
Posterior capsule opacification	1 (0.5)	-	1 (0.5)	4 (1.9)	-	4 (1.9)	5 (2.4)
Conjunctival haemorrhage	2 (1.0)	-	2 (1.0)	3 (1.4)	-	3 (1.4)	4 (1.9)
Eye irritation	2 (1.0)	-	2 (1.0)	1 (0.5)	-	1 (0.5)	3 (1.4)
Subretinal fluid	-	-	-	1 (0.5)	2 (1.0)	3 (1.4)	3 (1.4)
Cataract	-	-	-	2 (1.0)	-	2 (1.0)	2 (1.0)
Retinal pigment epithelial tear	-	-	-	2 (1.0)	1 (0.5)	2 (1.0)	2 (1.0)
Blepharitis	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Blindness transient	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)
Chalazion	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Dry eye	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Hypoaesthesia eye	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Lacrimation increased	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Ocular hyperaemia	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Retinal degeneration	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Retinal oedema	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)
Subretinal fibrosis	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Vitreous detachment	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Vitreous haemorrhage	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)
General disorders and administration site conditions	**4 (1.9)**	**3 (1.4)**	**7 (3.4)**	**-**	**-**	**-**	**7 (3.4)**
Drug ineffective	4 (1.9)	3 (1.4)	7 (3.4)	-	-	-	7 (3.4)
Infections and infestations	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Herpes zoster	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Injury, poisoning and procedural complications	**7 (3.4)**	**-**	**7 (3.4)**	**1 (0.5)**	**2 (1.0)**	**3 (1.4)**	**10 (4.8)**
Intraocular injection complication	7 (3.4)	-	7 (3.4)	1 (0.5)	2 (1.0)	3 (1.4)	10 (4.8)
Investigations	**-**	**-**	**-**	**-**	**1 (0.5)**	**1 (0.5)**	**1 (0.5)**
Intraocular pressure increased	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)

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Table 10-27: Adverse events in the context of the study eye by SOC and PT (in nAMD patients treated with brolucizumab or ranibizumab)

SAF (N=207)	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
SOC (MedDRA v24.0 to v26.0) **PT**							
Musculoskeletal and connective tissue disorders	**-**	**-**	**-**	**1 (0.5)**	**-**	**1 (0.5)**	**1 (0.5)**
Sjogren's syndrome	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Nervous system disorders	**-**	**-**	**-**	**-**	**1 (0.5)**	**1 (0.5)**	**1 (0.5)**
Headache	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SAF = Safety Analysis Set, SOC = System Organ Class
Seriousness assessed with 'yes' by physicians or pharmacovigilance.
Causality of ADRs referred to treatment with brolucizumab or ranibizumab.
AEs without information on relation or seriousness were considered as related or serious.
Primary SOCs were presented alphabetically. PTs were sorted within primary SOC by descending frequency order in any AE.
A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A subject with multiple adverse events within a primary SOC was counted only once in the total row.

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Table 10-28: Adverse events in the context of the fellow eye by SOC and PT (in nAMD patients treated with brolucizumab or ranibizumab)

SAF (N=207)	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
SOC (MedDRA v24.0 to v26.0) **PT**							
Number of patients with at least one AE, n (%)	**11 (5.3)**	**3 (1.4)**	**12 (5.8)**	**10 (4.8)**	**2 (1.0)**	**12 (5.8)**	**18 (8.7)**
Eye disorder	**10 (4.8)**	**-**	**10 (4.8)**	**8 (3.9)**	**2 (1.0)**	**10 (4.8)**	**16 (7.7)**
Posterior capsule opacification	1 (0.5)	-	1 (0.5)	5 (2.4)	-	5 (2.4)	6 (2.9)
Eye pain	3 (1.4)	-	3 (1.4)	-	-	-	3 (1.4)
Conjunctival haemorrhage	-	-	-	2 (1.0)	-	2 (1.0)	2 (1.0)
Neovascular age-related macular degeneration	1 (0.5)	-	1 (0.5)	1 (0.5)	-	1 (0.5)	2 (1.0)
Blepharitis	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Cataract	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Conjunctival oedema	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Dry eye	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Eye irritation	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Retinal deposits	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Retinal drusen	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Retinal oedema	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)
Retinal tear	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Subretinal fluid	-	-	-	-	1 (0.5)	1 (0.5)	1 (0.5)
General disorders and administration site conditions	**-**	**3 (1.4)**	**3 (1.4)**	**-**	**-**	**-**	**3 (1.4)**
Drug ineffective	-	3 (1.4)	3 (1.4)	-	-	-	3 (1.4)
Infections and infestations	**2 (1.0)**	**-**	**2 (1.0)**	**-**	**-**	**-**	**2 (1.0)**
Conjunctivitis	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Hordeolum	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Injury, poisoning and procedural complications	**3 (1.4)**	**-**	**3 (1.4)**	**-**	**-**	**-**	**3 (1.4)**
Intraocular injection complication	3 (1.4)	-	3 (1.4)	-	-	-	3 (1.4)
Periorbital haematoma	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Musculoskeletal and connective tissue disorders	**-**	**-**	**-**	**1 (0.5)**	**-**	**1 (0.5)**	**1 (0.5)**
Sjogren's syndrome	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)

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Table 10-28: Adverse events in the context of the fellow eye by SOC and PT (in nAMD patients treated with brolucizumab or ranibizumab)

SAF (N=207)	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
SOC (MedDRA v24.0 to v26.0) **PT**							
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (1.0)**	**-**	**2 (1.0)**	**1 (0.5)**	**-**	**1 (0.5)**	**2 (1.0)**
Basal cell carcinoma	1 (0.5)	-	1 (0.5)	1 (0.5)	-	1 (0.5)	1 (0.5)
Blepharal papilloma	1 (0.5)	-	1 (0.5)	-	-		1 (0.5)

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SAF = Safety Analysis Set, SOC = System Organ Class
Seriousness assessed with 'yes' by physicians or pharmacovigilance.
Causality of ADRs referred to treatment with brolucizumab or ranibizumab.
AEs without information on relation or seriousness were considered as related or serious.
Primary SOCs were presented alphabetically. PTs were sorted within primary SOC by descending frequency order in any AE.
A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A subject with multiple adverse events within a primary SOC was counted only once in the total row.

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Table 10-29: Non-ocular adverse events by SOC and PT (in nAMD patients treated with brolucizumab or ranibizumab)

SAF (N=207)	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
SOC (MedDRA v24.0 to v26.0) **PT**							
Number of patients with at least one AE, n (%)	**13 (6.3)**	**-**	**13 (6.3)**	**11 (5.3)**	**-**	**11 (5.3)**	**21 (10.1)**
Cardiac disorders	**1 (0.5)**	**-**	**1 (0.5)**	**3 (1.4)**	**-**	**3 (1.4)**	**4 (1.9)**
Aortic valve stenosis	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Cardiovascular disorder	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Coronary artery occlusion	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Myocardial infarction	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Gastrointestinal disorders	**1 (0.5)**	**-**	**1 (0.5)**	**-**	**-**	**-**	**1 (0.5)**
Abdominal pain upper	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
General disorders and administration site conditions	**-**	**-**	**-**	**2 (1.0)**	**-**	**2 (1.0)**	**2 (1.0)**
Death	-	-	-	2 (1.0)	-	2 (1.0)	2 (1.0)
Infections and infestations	**5 (2.4)**	**-**	**5 (2.4)**	**-**	**-**	**-**	**5 (2.4)**
COVID-19	4 (1.9)	-	4 (1.9)	-	-	-	4 (1.9)
Nasopharyngitis	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Injury, poisoning and procedural complications	**3 (1.4)**	**-**	**3 (1.4)**	**3 (1.4)**	**-**	**3 (1.4)**	**5 (2.4)**
Fall	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Intraocular injection complication	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Shoulder fracture	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Thoracic vertebral fracture	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Upper limb fracture	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Wrist fracture	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Investigations	**-**	**-**	**-**	**2 (1.0)**	**-**	**2 (1.0)**	**2 (1.0)**
Heart rate decreased	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Heart rate irregular	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Metabolism and nutrition disorders	**-**	**-**	**-**	**1 (0.5)**	**-**	**1 (0.5)**	**1 (0.5)**
Type 2 diabetes mellitus	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Musculoskeletal and connective tissue disorders	**1 (0.5)**	**-**	**1 (0.5)**	**-**	**-**	**-**	**1 (0.5)**
Back pain	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Nervous system disorders	**3 (1.4)**	**-**	**3 (1.4)**	**-**	**-**	**-**	**3 (1.4)**
Dementia	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Headache	2 (1.0)	-	2 (1.0)	-	-	-	2 (1.0)

Table 10-29: Non-ocular adverse events by SOC and PT (in nAMD patients treated with brolucizumab or ranibizumab)

SAF (N=207)	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
SOC (MedDRA v24.0 to v26.0) **PT**							
Psychiatric disorders	**1 (0.5)**	**-**	**1 (0.5)**	**-**	**-**	**-**	**1 (0.5)**
Confusional state	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Respiratory, thoracic and mediastinal disorders	**1 (0.5)**	**-**	**1 (0.5)**	**1 (0.5)**	**-**	**1 (0.5)**	**2 (1.0)**
Dyspnoea exertional	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)
Epistaxis	1 (0.5)	-	1 (0.5)	-	-	-	1 (0.5)
Vascular disorders	**-**	**-**	**-**	**1 (0.5)**	**-**	**1 (0.5)**	**1 (0.5)**
Hypertensive crisis	-	-	-	1 (0.5)	-	1 (0.5)	1 (0.5)

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SAF = Safety Analysis Set, SOC = System Organ Class
Seriousness assessed with 'yes' by physicians or pharmacovigilance.
Causality of ADRs referred to treatment with brolucizumab or ranibizumab.
AEs without information on relation or seriousness were considered as related or serious.
Primary SOCs were presented alphabetically. PTs were sorted within primary SOC by descending frequency order in any AE.
A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A subject with multiple adverse events within a primary SOC was counted only once in the total row.

All-Cause Mortality

Two SAEnr with fatal outcome were reported. These referred to an 82-year old male patient and a 92-year old female patient. For both patients the verbatim SAEnr term “death of the subject” (PT: “Death”, MedDRA SOC: “General disorders and administration site conditions”) was reported.

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Serious Adverse Events

SAF (N=207)	Non-ocular	Study eye	Fellow eye	Any AE
Number of patients with at least one AE, n (%)	**21 (10.1)**	**28 (13.5)**	**18 (8.7)**	**46 (22.2)**
SAE	11 (5.3)	16 (7.7)	12 (5.8)	30 (14.5)
SADR	-	6 (2.9)	2 (1.0)	6 (2.9)
SAEnr	11 (5.3)	11 (5.3)	10 (4.8)	27 (13.0)
Number of events (overall)	**31**	**63**	**36**	**114**
SAE	14	30	14	54
SADR	0	10	2	10
SAEnr	14	20	12	44

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, nr = not related, ns = non-serious, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SAF = Safety Analysis Set

Seriousness assessed with 'yes' by physicians or pharmacovigilance.

Causality of ADRs referred to treatment with brolucizumab or ranibizumab.

AEs without information on relation or seriousness were considered as related or serious.

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Other (Not Including Serious) Adverse Events

SAF (N=207)	Non-ocular	Study eye	Fellow eye	Any AE
Number of patients with at least one AE, n (%)	**21 (10.1)**	**28 (13.5)**	**18 (8.7)**	**46 (22.2)**
nsAE	13 (6.3)	15 (7.2)	12 (5.8)	28 (13.5)
nsADR	-	3 (1.4)	3 (1.4)	3 (1.4)
nsAEnr	13 (6.3)	15 (7.2)	11 (5.3)	28 (13.5)
Number of events (overall)	**31**	**63**	**36**	**114**
nsAE	17	33	22	60
nsADR	0	3	3	3
nsAEnr	17	30	19	57

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, nr = not related, ns = non-serious, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SAF = Safety Analysis Set
Seriousness assessed with 'yes' by physicians or pharmacovigilance.
Causality of ADRs referred to treatment with brolucizumab or ranibizumab.
AEs without information on relation or seriousness were considered as related or serious.

Other Relevant Findings

Not applicable

Conclusion:

The results indicate that differences/benefits of Artificial Intelligence (AI) are difficult to prove. The data management platform Discovery®, embedded with a set of advanced AI algorithms, in clinical routine practice might support disease activity assessment and clinical workflow in neovascular Age-related Macular Degeneration (nAMD) patients. Furthermore, brolucizumab showed positive anatomical retinal fluid outcomes but the patient numbers for this analysis were low. Positive benefit-risk profile of brolucizumab and ranibizumab for patients with nAMD remains unchanged, no new safety signals were detected.

Date of Clinical Trial Report

28 March 2024