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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab

Trial Indication(s)

Neovascular Age-related Macular Degeneration (nAMD)

Protocol Number

CRTH258AAE01

Protocol Title

Effectiveness of brolucizumab in pretreated patients with nAMD in the real-world setting in Gulf countries United Arab of Emirates, Kuwait , Bahrain , Oman and Qatar

Clinical Trial Phase

Phase IV

Phase of Drug Development

Approval

Study Start/End Dates

Study Start Date: April 13, 2022 (Actual)

Primary Completion Date: March 13, 2023(Actual)
Study Completion Date: March 13, 2023(Actual)

Reason for Termination (If applicable)

Sponsor Decision

Study Design/Methodology

The study was a prospective and retrospective, observational, single-arm, non-randomized cohort study of ocular treatment with intravitreal injections of brolucizumab in nAMD patients.

This study was conducted prospectively and retrospectively. it aimed to include 99 nAMD patients who had their first brolucizumab injection before study start. Patients were planned to be enrolled from Gulf countries.

Patients who received brolucizumab before the study start were recruited into the study and signed an informed consent form at their first visit. Their index date was the date of their first brolucizumab injection, which have occurred during the recruitment period or in 6 months prior to their first visit. Patient history and characteristics were recorded in the 12 months prior to the index date.

The study period was between May-2020 and Nov-2023 to allow 6-month pre-index period and at least a 12-month follow-up period for each recruited patient.

Retrospective data was collected for all patients starting treatment with brolucizumab for up to 12 months before baseline (data included, but not limited to, number of anti-VEGF injections in treatment switch patients, VA and CST during the entire pre-index period, number of visits with presence of IRF/SRF/sub-retinal pigment epithelium (RPE), IRF/SRF/sub-RPE present (yes/no) at the time of switch, etc.). In addition, retrospective data collected during the pre-index period also collected for characterization and treatment history of patients.

The first patient was included on 03 October 2022 and the last patient on 04 October 2022. Due to the decision to premature termination of this study 0n 31 May 2023, the observational period per patient was reduced to 6 months. The last visit of the last patient took place on 07 March 2023.

In total, Three patients diagnosed with neovascular age-related macular degeneration (nAMD) and treated with the anti-VEGF brolucizumab injection as per local clinical practice were enrolled from one site Cleveland Clinic Abu Dhabi United Arabe Emirates . The three patients were included in the full analysis.

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Centers

One site in Cleveland Clinic Abu Dhabi United Arabe Emirates

Objectives:

The main questions the present study is expected to answer are:
• What is the fluid resolution at Month 12 after start of brolucizumab treatment in real-life patients?
• What are the characteristics, medical and treatment history of patients initiating brolucizumab in the real world?

Primary objective:
1. To evaluate fluid resolution (absence of intra-retinal fluid (IRF) and absence of subretinal fluid (SRF)) at Month 12 after initiation of brolucizumab in real-world patients.

Secondary objectives:
2. To characterize nAMD pre-treated patients who initiated treatment with brolucizumab with respect to baseline characteristics and patient history.

3. To evaluate anatomical parameters during treatment with brolucizumab.

4. To estimate VA change from baseline during treatment with brolucizumab.

5. To estimate the number of anti-VEGF injections, number of non-injection visits and total number of visits during treatment with brolucizumab, as well as last recorded injection interval at Month 6 and Month 12, and the percentage (%) of patients with anti-VEGF injection intervals ≤ 8 weeks (q8w) and ≥ 12 weeks (q12w) up to Month 12 of treatment with brolucizumab.

6. To estimate the number of OCT during treatment with brolucizumab, number of visits with/without OCT and assess their association with and choroidal neovascularization (CNV) activity and VA.

7. To explore the predictive value of age, baseline VA, baseline CNV activity, [active, active (SRF only), inactive], complete loading phase (yes/no), presence or not of IRF and SRF at baseline, VA at the end of the loading phase (Month 3), CNV activity at the end of the loading phase, [active, active (SRF only), inactive], number of anti-VEGF injections (maintenance phase), comorbidities, type and duration of previous anti-VEGF treatment on the VA gains at Month 12 of treatment with brolucizumab.

8. To assess criteria for no retreatment.

9. To estimate the percentage (%) of patients switching to another anti-VEGF during treatment with brolucizumab and characterize switchers with respect to their baseline characteristics at index date (baseline) and during the pre-switching period, reason for

switching, VA gain since start of brolucizumab, IRF and SRF at time of switch, duration of brolucizumab treatment before switch, last injection interval before switch.

10. To estimate discontinuation rate in nAMD treatment switchers receiving brolucizumab during 12 months of therapy and estimate the time to discontinuation.
11. To assess safety: number and nature of AEs, causes, severity, duration, treatment, resolution and vision loss associated with it.

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

Brolucizumab intravitreal injection

Statistical Methods

For all variables and all objectives, summary statistics included using the mean±standard deviation (sd), median along with min and max for numeric variables. For categorical variables, the frequency distribution was presented. No confidence intervals nor statistical tests were done due to the small sample size of the study.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Diagnosis of nAMD
- Patients with ≥18 years of age at index
- Receipt of at least one injection of brolucizumab (not necessarily the first one) during the index period
- Signed informed consent

Exclusion Criteria:

- Patients treated for retinal vein occlusion (RVO), diabetic macular edema (DME), myopic choroidal neovascularization (mCNV), and have diagnoses of diabetes-related macular degeneration within 6 months prior to the index date

• Receipt of any anti-VEGF treatment other than brolucizumab in the study eye during the index period

• Receipt of brolucizumab in the study eye more than 6 months before the index period, i.e., brolucizumab treatment started more than 6 months before the start of the study

• Any active intraocular or periocular infection or active intraocular inflammation in the study eye at index date

• Patients who have any contraindication and are not eligible for treatment with brolucizumab as according to the label

• Patients who were treated with more than 2 types of anti-VEGF before index date (4th line brolucizumab patients or more)

• Any medical or psychological condition in the treating physician's opinion which may prevent the patient from the 12-month study participation

• Patients participating in parallel in an interventional clinical trial

Note: if a patient experiences an adverse event (AE), they may still be recruited in another study following this AE if they fulfill their inclusion criteria. Their data will still be collected as planned by the current protocol

• Patients participating in parallel in any other NIS generating primary data for an anti-VEGF drug

Participant Flow Table

Number of participants	**n(%)**
Started	3 (100%)
3 month visit	3 (100%)
6 month visit	3 (100%)
9 month visit	1 (33.3%)
Completed	0 (0%)
Reason for discontinuation	
Study prematurely terminated	3 (100%)

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Baseline Characteristics

Variable		n(%)
AGE	mean±sd	66.7±4.9
	median	69
	min-max	61-70
Gender	Female	2 (66.7%)
	Male	1 (33.3%)
Ethnicity	Arab	3 (100%)
Weight (in kg)	mean±sd	78±0
(n=1)	median	78

	min-max	78-78
Insurance	Public	3 (100%)
Smoking (n=1)	Never	1(100.0%)

Primary Outcome Result(s)

1. **Percentage of patients with absence of Subretinal Fluid (SRF) and Intra-Retinal Fluid (IRF) at Month 12**

The percentage of treated patients with absence of SRF and IRF cannot be provided. The study prematurely terminated before Month 12 follow up period after brolucizumab initiation.

Secondary Outcome Result(s)

2. **Percentage of patients ≥ 80 years old**

No patients were over 80 years old in this study.

3. **Duration of diagnosis**

Variable		n(%)
Unilateral AMD	Yes	0 (0.0%)

Time since first diagnosis (in years)	mean±sd	1.7±2.9
	median	0
	min-max	0-5
Time between diagnosis and first treatment (in months)	mean±sd	20.0±34.6
	median	0
	min-max	0-60

4. **Percentage of patients with baseline visit**

Variable	n(%)
Baseline visit	3 (100%)

5. **Percentage of patients with bilateral disease**

Variable	n(%)
Patients with bilateral disease	3 (100%)

6. **Percentage of patients with lesion type**

Variable		n(%)
Lesion type	Predominantly Classic	1 (33.3%)
	Occult	1 (33.3%)
	Other	1 (33.3%)

7. Percentage of patients with presence or absence of Subretinal Fluid (SRF), Intra-Retinal Fluid (IRF) and sub- Retinal Pigment Epithelium (RPE)

Variable	n(%)	Variable
Intra-Retinal Fluid (IRF)	Absent	2(66.7%)
	Present	1(33.3%)
Subretinal Fluid (SRF)	Absent	1(33.3%)
	Present	2(66.7%)
Sub-RPE fluid	Present	3(100.0%)

8. Baseline Central Subfield Thickness (CST)

Variable		n(%)
Central Subfield Thickness (CST)	Not available	3(100.0%)

9. Baseline Visual Acuity (VA)

Variable	n(%)	Variable
Visual Acuity (Early Treatment Diabetic Retinopathy Study (ETDRS)) in study eye	Not available	3(100.0%)

10. Percentage of patients with the study eye that has Visual Acuity (VA) equal or less than the VA in fellow eye at baseline

Visual acuity data were not available at any of the visits.

11. Percentage of patients with baseline Visual Acuity (VA) in the following categories (≤35, 36-69, ≥ 70 ETDRS letters)

Visual acuity data were not available at any of the visits.

12. Percentage of patients with baseline Visual Acuity (VA) between 34 and 72 ETDRS letters

Visual acuity data were not available at any of the visits.

13. Percentage of patients with baseline Visual Acuity (VA) < 73 ETDRS letters and active (SRF only)

Visual acuity data were not available at any of the visits.

14. Switch Patients: Previous anti-VEGF treatments of nAMD pre-treated patients

Variable	n(%)

Previous anti-VEGF treatments other than brolucizumab	Yes	3(100.0%)
Number of previous anti-VEGF treatments	1	3(100.0%)
Name of previous anti-VEGF treatments	Ranibizumab	2 (66.7%)
	Aflibercept	1 (33.3%)
Reason for Switching	Anatomical	1 (33.3%)
	Functional	2 (66.7%)

15. Switch Patients: Duration of previous anti-VEGF treatments

Variable		n(%)
Duration of pervious anti-VEGF treatment (in months) (n=2)	mean±sd	2.2±0.2
	median	2.2
	min-max	2.1-2.3
Total Number of previous injections	3	1 (33.3%)
	6	1 (33.3%)
	Unknown	1 (33.3%)

16. Switch Patients: Number of injections in the last year before switching to brolucizumab

Variable		n(%)
Number of injections in the last year before switching to brolucizumab	3	1 (33.3%)
	6	1 (33.3%)
	Unknown	1 (33.3%)

17. Switch Patients: Last interval of anti-VEGF treatment before switching

Variable		n(%)
Total number of previous injections over last 6 months	0	1 (33.3%)
	6	1 (33.3%)
	Unknown	1 (33.3%)
Total number of previous injections over last 3 months	0	2 (66.7%)
	4	1 (33.3%)

18. Percentage of patients with absent, decrease or maintained Subretinal Fluid (SRF)

	3 Months Follow up		**6 Months Follow up**		**9 Months Follow up**	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**

SRF	Absent Decreased Maintained	 2(66.7%) 1(33.3%)	Absent Decreased Maintained	1(33.3%) 1(33.3%) 1(33.3%)	Not available	1(100.0%)

19. Percentage of patients with absent, decrease or maintained Intra-Retinal Fluid (IRF)

	3 Months Follow up		**6 Months Follow up**		**9 Months Follow up**	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
SRF	Absent Decreased Maintained	1(33.3%) 1(33.3%) 1(33.3%)	Absent Decreased Maintained	2(66.7%) 1(33.3%)	Not available	1(100.0%)

20. Percentage of patients with absent, decrease or maintained sub- Retinal Pigment Epithelium (RPE) Fluid

	3 Months Follow up		**6 Months Follow up**		**9 Months Follow up**	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
SRF	Absent Decreased Maintained	 2(66.7%) 1(33.3%)	Absent Decreased Maintained	1(33.3%) 1(33.3%) 1(33.3%)	Not available	1(100.0%)

21. Percentage of patients with absence of Subretinal Fluid (SRF), Intra-Retinal Fluid (IRF) and sub- Retinal Pigment Epithelium (RPE) and time to absence

Patient	Variable	Baseline	3 Months	6 months	time to absence
1	SRF	Present	Decreased	Decreased	
2		Absent	Maintained	Maintained	
3		Present	Decreased	Absent	5.72 months
1	IRF	Absent	Decreased	Absent	
2		Absent	Maintained	Maintained	
3		Present	Absent	Absent	3.45 months
1	sub-RPE	Present	Decreased	Decreased	
2		Present	Maintained	Maintained	
3		Present	Decreased	Absent	5.72 onths

22. Estimate Central Subfield Thickness (CST) change from baseline

	3 Months Follow up		6 Months Follow up		9 Months Follow up	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
Central Subfield Thickness (CST), µm	Not available	3(100%)	Not available	3(100%)	Not available	1(100.0%)

23. Percentage of patients with reduced Central Subfield Thickness (CST) vs baseline

CST values at Baseline were not available, therefore results for this endpoint could not be calculated.

24. Association between Central Subfield Thickness (CST) variability at Months 1-12 and Visual Acuity (VA) change from baseline

Visual acuity data were not available at any of the visits, which didn't allow for the assessment of association between CST variables and VA at different visits.

25. Association between Central Subfield Thickness (CST) variability at Months 1-12 and number of injections

Number of injections within specific time frames couldn't be collected as the dates of injections were not available, which didn't allow for the assessment of association between CST variables and number of injections.

26. Percentage of patients with clinician-graded subretinal fibrosis and/or macular atrophy at month 12

The percentage of treated patients with clinician-graded subretinal fibrosis and/or macular atrophy at month 12 cannot be provided. The study prematurely terminated before Month 12 follow up period.

27. Visual Acuity (VA) change from baseline

Visual acuity data were not available at any of the visits.

28. Percentage of patients with Visual Acuity (VA) change from baseline

Visual acuity data were not available at any of the visits.

29. Percentage of patients with ≥ 70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters

Visual acuity data were not available at any of the visits.

30. Follow-up Results - Number of brolucizumab visits

	3 Months Follow up		6 Months Follow up		9 Months Follow up	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
Time between first injection and follow up avisit (in months)	mean±sd median min-max	3.1±0.3 3.2 2.8-3.5	mean±sd median min-max	5.4±0.3 5.3 5.3-5.7	value	9.4
Still taking Brolucizumab	Yes	3(100.0%)	Yes	3(100.0%)	Yes	1(100.0%)
Number of non-injection visits since last study visit	0 1	1(33.3%) 2(66.7%)	 1	 3(100.0%)	 3	 1(100.0%)
Total number of visits since last study visit	2 3	1(33.3%) 2(66.7%)	2	3(100.0%)	 4	 1(100.0%)

31. Distribution of injection intervals

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

32. Percentage of patients with at least one duration of interval between injections

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

33. Percentage of patients with at least two consecutive duration of intervals between injections

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

34. Percentage of switch patients from other anti- Vascular Endothelial Growth Factor (VEGF) that prolonged injection intervals with brolucizumab

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

35. Percentage of patients with ≥ 3 brolucizumab injections

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

36. Number of participants by last recorded injection interval

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

37. Time between two consecutive brolucizumab injections

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

38. Number of visits with/without Optical Coherence Tomography (OCT)

	3 Months Follow up		**6 Months Follow up**		**9 Months Follow up**	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
Number of visits with/without OCT (among those with OCT)	1	1(50.0%)	2	2(66.7%)		
	2	1(50.0%)	4	1(33.3%)	4	1(100.0%)

39. Association between number of Optical Coherence Tomography (OCT) and Choroidal Neovascularization (CNV) activity

CNV activity at the end of the loading phase was not collected, therefore this endpoint could not be analyzed.

40. Association between number of Optical Coherence Tomography (OCT) and Visual Acuity (VA) change from baseline

Visual acuity data were not available at any of the visits, therefore the endpoint could not be analyzed.

41. Association between number of Optical Coherence Tomography (OCT) and number of injections

Number of injections within specific time frames couldn't be collected as the dates of injections were not available.

42. Proportion of participants by baseline Choroidal Neovascularization (CNV) activity

Variable	n(%)	Variable
Subtype of CNV	PCV	1(33.3%)
	Type I	1(33.3%)
	Type II	1(33.3%)

43. Proportion of participants with and without Loading phase

Proportion of participants with and without loading phase could not be calculated.

44. Visual Acuity (VA) at the end of the loading phase

VA at the end of the loading phase could not be calculated.

45. Choroidal Neovascularization (CNV) activity at the end of the loading phase

CNV at the end of the loading phase could not be calculated.

46. Number of injections during the maintenance phase

	3 Months Follow up		6 Months Follow up		9 Months Follow up	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
Number of injections since last study visit	2	3(100.0%)	1	3(100.0%)	1	1(100.0%)

47. Percentage of patients with geographic atrophy

	3 Months Follow up		6 Months Follow up		9 Months Follow up	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**
Geographic Atrophy	No Yes	2(66.7%) 1(33.3%)	No Yes	2(66.7%) 1(33.3%)	Not available	1(100.0%)

48. Percentage of patients with subretinal fibrosis

	3 Months Follow up		6 Months Follow up		9 Months Follow up	
Variable	**N=3**	**n(%)**	**N=3**	**n(%)**	**N=1**	**n(%)**

Subretinal fibrosis	No Yes	2(66.7%) 1(33.3%)	No Yes	2(66.7%) 1(33.3%)	Not available	1(100.0%)

49. Assessment of criteria for no retreatment

De to the early termination of the trial, data for this endpoint could not be collected.

50. Percentage of patients who switch to another anti-VEGF

No data of patients switching to another anti-VEGF was collected.

51. Visual Acuity (VA) at time of switch

No data of patients switching to another anti-VEGF was collected.

52. Percentage of patients with activity at time of switch

No data of patients switching to another anti-VEGF was collected.

53. Percentage of switchers with full loading phase

No data of patients switching to another anti-VEGF was collected.

54. Percentage of patients by injection rate at pre-switch period

No data of patients switching to another anti-VEGF was collected.

55. Reason for switching to another anti- Vascular Endothelial Growth Factor (VEGF)

No data of patients switching to another anti-VEGF was collected.

56. Last recorded injection interval before switching

No data of patients switching to another anti-VEGF was collected.

57. Duration of brolucizumab treatment before switching

No data of patients switching to another anti-VEGF was collected.

58. Percentage of patients who discontinue therapy.

All 3 patients discontinued due to the early termination of the trial.

59. Days of persistence.

Due to the early termination of the trial this endpoint could not be calculated.

60. Percentage of patients with Adverse Events (AEs)

No Adverse event was reported in this study.

61. Adverse Event (AE) rate

No Adverse event was reported in this study.

Other Pre-Specified Outcome Result(s)

Not applicable.

Post-Hoc Outcome Result(s)

Not applicable

Safety Results

There were no Adverse events reported throughout the study

All-Cause Mortality

There was no death in this study

Serious Adverse Events

There were no Serious adverse events reported throughout the study

Other (Not Including Serious) Adverse Events

There were no Serious adverse events reported throughout the study

Other Relevant Findings

Not applicable

Conclusion:

Due to early study termination, there is no enough data to assess the effectiveness of brolucizumab in pretreated patients with Neovascular Age-related Macular Degeneration (nAMD) in the real-world setting in Gulf countries. However the results of the 3 patients over the 6 months Follow up showed a promising safety profile as no Adverse event was reported and all the patients continuing taking the Brolucizumab.

Date of Clinical Trial Report

12 March 2024