



Clinical trial results:

An Open-Label Safety Study of Retinal Gene Therapy for Choroideremia with Bilateral, Sequential Administration of Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)

Summary

EudraCT number	2017-002395-75
Trial protocol	DE FR
Global end of trial date	29 June 2022

Results information

Result version number	v1
This version publication date	15 July 2023
First version publication date	15 July 2023

Trial information

Trial identification

Sponsor protocol code	273CH203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03507686
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: NSR-REP-02

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Stretet, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to evaluate the safety of bilateral, sequential sub-retinal administration of a single dose of BIIB111 in adult male participants with Choroideremia (CHM).

Protection of trial subjects:

Written informed consent was obtained from each participant or participant`s legally authorized representative, as applicable, prior to evaluations performed for eligibility. Participants or the participant`s legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	France: 2
Worldwide total number of subjects	66
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	64

From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at the investigative sites in the France, Germany, and the United States from 29 November 2017 to 29 June 2022.

Pre-assignment

Screening details:

66 unique male participants with Choroideremia were treated in study. Of which 60 participants were treated in Period 1, 50 participants completed Period 1. 50 participants from Period 1 enrolled in Period 2 along with 6 unique participants who were treated in first eye in previous study (20150371, THOR-TUE-01). 53 participants completed Period 2.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Treated Subjects
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Arm description:

After vitrectomy and retinal detachment in the study eye 1 and study eye 2, participants received a single administration of BIIB111, 1×10^{11} genome particles (gp), as a sub-retinal injection on Day 0 (surgery day) of Period 1 and Period 2, respectively.

Arm type	Experimental
Investigational medicinal product name	BIIB111
Investigational medicinal product code	
Other name	AAV2-REP1
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraocular use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	All Treated Subjects
Started	66
Completed	53
Not completed	13
Adverse event, serious fatal	1
Consent withdrawn by subject	2
Serious Adverse event	4
Site Terminated by Sponsor	2
Reason not Specified	4

Baseline characteristics

Reporting groups

Reporting group title	All Treated Subjects
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Reporting group description:

After vitrectomy and retinal detachment in the study eye 1 and study eye 2, participants received a single administration of BIIB111, 1×10^{11} genome particles (gp), as a sub-retinal injection on Day 0 (surgery day) of Period 1 and Period 2, respectively.

Reporting group values	All Treated Subjects	Total	
Number of subjects	66	66	
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	36.7 ± 13.57	-	
Gender categorical Units: Subjects			
Male	66	66	
Female	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	60	60	
Unknown or Not Reported	2	2	
Race Units: Subjects			
Asian	1	1	
White	65	65	

Subject analysis sets

Subject analysis set title	Treatment Period 1: BIIB111
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

After vitrectomy and retinal detachment in the study eye 1, participants received a single administration of BIIB111, 1×10^{11} gp, as a sub-retinal injection on Day 0 (surgery day) of Period 1.

Subject analysis set title	Treatment Period 2: BIIB111
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

After vitrectomy and retinal detachment in the study eye 2, participants received a single administration of BIIB111, 1×10^{11} gp, as a sub-retinal injection on Day 0 (surgery day) of Period 2.

Reporting group values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111	
Number of subjects	60	56	

Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	0 ±	0 ±	
Gender categorical Units: Subjects			
Male	0	0	
Female	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	0	0	
Unknown or Not Reported	0	0	
Race Units: Subjects			
Asian	0	0	
White	0	0	

End points

End points reporting groups

Reporting group title	All Treated Subjects
Reporting group description: After vitrectomy and retinal detachment in the study eye 1 and study eye 2, participants received a single administration of BIIB111, 1×10^{11} genome particles (gp), as a sub-retinal injection on Day 0 (surgery day) of Period 1 and Period 2, respectively.	
Subject analysis set title	Treatment Period 1: BIIB111
Subject analysis set type	Intention-to-treat
Subject analysis set description: After vitrectomy and retinal detachment in the study eye 1, participants received a single administration of BIIB111, 1×10^{11} gp, as a sub-retinal injection on Day 0 (surgery day) of Period 1.	
Subject analysis set title	Treatment Period 2: BIIB111
Subject analysis set type	Intention-to-treat
Subject analysis set description: After vitrectomy and retinal detachment in the study eye 2, participants received a single administration of BIIB111, 1×10^{11} gp, as a sub-retinal injection on Day 0 (surgery day) of Period 2.	

Primary: Mean Best-Corrected Visual Acuity (BCVA) as Measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart in Letters at Month 12

End point title	Mean Best-Corrected Visual Acuity (BCVA) as Measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart in Letters at Month 12 ^[1]
End point description: BCVA was assessed for both eyes using the ETDRS visual acuity (VA) chart. BCVA test should be performed prior to pupil dilation, and distance refraction should be carried out before BCVA is measured. Initially, letters are read at a distance of 4 meters from the chart. If <20 letters are read at 4 meters, testing at 1 meter should be performed. BCVA is reported as number of letters read correctly by the participant using the ETDRS Scale (ranging from 0 to 100 letters) in the study eyes. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). An increase in the number of letters read correctly means that vision has improved. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of Subjects analysed' indicates the number of participants with data available for endpoint analysis.	
End point type	Primary
End point timeframe: Month 12	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned or performed for this endpoint.	

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: letters				
arithmetic mean (standard deviation)				
Study Eye 1	68.0 (± 25.18)	76.5 (± 13.78)		
Study Eye 2	82.3 (± 8.67)	81.2 (± 10.82)		

Statistical analyses

No statistical analyses for this end point

Primary: Ophthalmic Examination Assessment: Mean Intraocular Pressure (IOP) at Month 12

End point title	Ophthalmic Examination Assessment: Mean Intraocular Pressure (IOP) at Month 12 ^[2]
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End point description:

IOP, the fluid pressure inside the eye was measured and reported in mmHg. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	52		
Units: millimetres mercury (mmHg)				
arithmetic mean (standard deviation)				
Study Eye 1	13.5 (± 3.09)	13.5 (± 3.12)		
Study Eye 2	14.9 (± 2.50)	13.5 (± 3.55)		

Statistical analyses

No statistical analyses for this end point

Primary: Ophthalmic Examination Assessment: Number of Participants With Clinically Significant Abnormalities in Slit Lamp Examination

End point title	Ophthalmic Examination Assessment: Number of Participants With Clinically Significant Abnormalities in Slit Lamp Examination ^[3]
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End point description:

Slit lamp examinations of study eyes included examination of Cornea, Conjunctiva, Iris, Lens, and Anterior Segment. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified category at specified timepoint.

End point type	Primary
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End point timeframe:

Baseline, Month 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	56		
Units: participants				
Cornea: Study Eye 1: Baseline	0	0		
Cornea: Study Eye 1: Month 12 (n=15,53)	0	0		
Cornea: Study Eye 2: Baseline	0	0		
Cornea: Study Eye 2: Month 12 (n=15,53)	0	0		
Conjunctiva: Study Eye 1: Baseline	0	1		
Conjunctiva: Study Eye 1: Month 12 (n=15,53)	0	0		
Conjunctiva: Study Eye 2: Baseline	0	0		
Conjunctiva: Study Eye 2: Month 12 (n=15,53)	0	0		
Iris: Study Eye 1: Baseline	0	0		
Iris: Study Eye 1: Month 12 (n=15,53)	0	0		
Iris: Study Eye 2: Baseline	0	0		
Iris: Study Eye 2: Month 12 (n=15,53)	0	0		
Lens: Study Eye 1: Baseline	2	2		
Lens: Study Eye 1: Month 12 (n=15,53)	1	4		
Lens: Study Eye 2: Baseline	2	2		
Lens: Study Eye 2: Month 12 (n=15,53)	0	3		
Anterior Segment: Study Eye 1: Baseline	0	0		
Anterior Segment: Study Eye 1: Month 12 (n=15,53)	0	0		
Anterior Segment: Study Eye 2: Baseline	0	0		
Anterior Segment: Study Eye 2: Month 12 (n=15,53)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Ophthalmic Examination Assessment: Number of Participants With Clinically Significant Abnormalities in Dilated Ophthalmoscopy

End point title	Ophthalmic Examination Assessment: Number of Participants With Clinically Significant Abnormalities in Dilated Ophthalmoscopy ^[4]
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End point description:

Dilated Ophthalmoscopy examination of study eyes included examination of Vitreous, Macula, Peripheral retina, Choroid, and Optic nerve. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified category at specified timepoint.

End point type	Primary
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End point timeframe:

Baseline, Month 12

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	56		
Units: participants				
Vitreous: Study Eye 1: Baseline	0	0		
Vitreous: Study Eye 1: Month 12 (n=15,53)	1	1		
Vitreous: Study Eye 2: Baseline	0	0		
Vitreous: Study Eye 2: Month 12 (n=15,53)	0	1		
Macula: Study Eye 1: Baseline	57	54		
Macula: Study Eye 1: Month 12 (n=15,53)	15	51		
Macula: Study Eye 2: Baseline	58	54		
Macula: Study Eye 2: Month 12 (n=15,53)	15	51		
Peripheral Retina: Study Eye 1: Baseline	58	54		
Peripheral Retina: Study Eye 1:Month 12 (n=15,53)	15	51		
Peripheral Retina: Study Eye 2: Baseline	58	54		
Peripheral Retina: Study Eye 2:Month 12 (n=15,53)	15	51		
Choroid: Study Eye 1: Baseline	58	54		
Choroid: Study Eye 1: Month 12 (n=15,53)	15	51		
Choroid: Study Eye 2: Baseline	58	54		
Choroid: Study Eye 2: Month 12 (n=15,53)	15	51		
Optic Nerve: Study Eye 1: Baseline	5	4		
Optic Nerve: Study Eye 1: Month 12 (n=15,53)	0	3		
Optic Nerve: Study Eye 2: Baseline	6	4		
Optic Nerve: Study Eye 2: Month 12 (n=15,53)	0	4		

Statistical analyses

No statistical analyses for this end point

Primary: Ophthalmic Examination Assessment: Number of Participants With Lens Opacity Grading

End point title	Ophthalmic Examination Assessment: Number of Participants With Lens Opacity Grading ^[5]
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End point description:

The following lens opacity grades are reported for categories 1-4: Nuclear Opalescence grade, Nuclear Color grade, Cortical Cataract grade, and Posterior Cataract grade. Category 1 includes values 1, 1.0 and 0.x, Category 2 includes values 2, 2.0 and 1.x, Category 3 includes values 3, 3.0 and 2.x, and Category 4 includes values 4, 4.0, 3.x and any values above 4. All Treated Subjects analysis set

included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified category of specified parameter.

End point type	Primary
End point timeframe:	
Month 12	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: participants				
NuclearOpalescenceGrade:Category1:Eye1(n=14,50)	13	38		
NuclearOpalescenceGrade:Category 2:Eye1(n=14,50)	1	8		
NuclearOpalescenceGrade:Category 3:Eye1(n=14,50)	0	4		
NuclearOpalescenceGrade: Category 4:Eye1(N=14,50)	0	0		
Nuclear Opalescence Grade: Category 1: Study Eye 2	14	38		
Nuclear Opalescence Grade: Category 2: Study Eye 2	1	10		
Nuclear Opalescence Grade: Category 3: Study Eye 2	0	2		
Nuclear Opalescence Grade: Category 4: Study Eye 2	0	0		
Nuclear Color Grade:Category 1:Study Eye1(n=14,50)	14	41		
Nuclear Color Grade:Category 2:Study Eye1(n=14,50)	0	5		
Nuclear Color Grade:Category 3:Study Eye1(n=14,50)	0	4		
NuclearColorGrade:Category 4:Study Eye 1 (n=14,50)	0	0		
Nuclear Color Grade: Category 1: Study Eye 2	15	41		
Nuclear Color Grade: Category 2: Study Eye 2	0	7		
Nuclear Color Grade: Category 3: Study Eye 2	0	2		
Nuclear Color Grade: Category 4: Study Eye 2	0	0		
Cortical CataractGrade:Category1:Eye1(n=14,50)	13	43		
Cortical CataractGrade:Category2:Eye1(n=14,50)	1	5		
Cortical CataractGrade:Category3:Eye1(n=14,50)	0	2		
Cortical CataractGrade:Category4:Eye1(n=14,50)	0	0		
Cortical Cataract Grade: Category 1: Study Eye 2	14	44		

Cortical Cataract Grade: Category 2: Study Eye 2	1	6		
Cortical Cataract Grade: Category 3: Study Eye 2	0	0		
Cortical Cataract Grade: Category 4: Study Eye 2	0	0		
PosteriorCataractGrade:Category1:Eye1 (n=14,50)	13	40		
PosteriorCataractGrade:Category2:Eye1 (n=14,50)	0	6		
PosteriorCataractGrade:Category3:Eye1 (n=14,50)	0	3		
PosteriorCataractGrade:Category4:Eye1 (n=14,50)	1	1		
Posterior Cataract Grade: Category 1: Study Eye 2	15	44		
Posterior Cataract Grade: Category 2: Study Eye 2	0	6		
Posterior Cataract Grade: Category 3: Study Eye 2	0	0		
Posterior Cataract Grade: Category 4: Study Eye 2	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Spectral Domain Optical Coherence Tomography (SD-OCT): Foveal Subfield Thickness at Month 12

End point title	Spectral Domain Optical Coherence Tomography (SD-OCT): Foveal Subfield Thickness at Month 12 ^[6]
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End point description:

SD-OCT was used to assess change in foveal subfield thickness. The measurements were taken after dilation of the participant's pupil. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: microns (μ)				
arithmetic mean (standard deviation)				
Study Eye 1	290.7 (± 69.94)	258.0 (± 58.20)		
Study Eye 2	283.8 (± 46.65)	270.9 (± 51.66)		

Statistical analyses

No statistical analyses for this end point

Primary: SD-OCT: Total Macular Volume at Month 12

End point title	SD-OCT: Total Macular Volume at Month 12 ^[7]
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End point description:

SD-OCT was used to assess change in total macular volume. The measurements were taken after dilation of the participant's pupil. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: cubic millimetres (mm ³)				
arithmetic mean (standard deviation)				
Study Eye 1 (n=14, 53)	6.770 (± 1.1384)	6.638 (± 1.0934)		
Study Eye 2	6.903 (± 1.0875)	6.741 (± 1.1616)		

Statistical analyses

No statistical analyses for this end point

Primary: SD-OCT: Central Ellipsoid Area at Month 12

End point title	SD-OCT: Central Ellipsoid Area at Month 12 ^[8]
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End point description:

SD-OCT was used to assess change in central ellipsoid area. The measurements were taken after dilation of the participant's pupil. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	28		
Units: square millimetres (mm ²)				
arithmetic mean (standard deviation)				
Study Eye 1 (n=7, 25)	3.213 (± 2.1098)	2.971 (± 1.7374)		
Study Eye 2	4.404 (± 2.2848)	3.810 (± 2.5563)		

Statistical analyses

No statistical analyses for this end point

Primary: SD-OCT: Central Horizontal Ellipsoid Width at Month 12

End point title	SD-OCT: Central Horizontal Ellipsoid Width at Month 12 ^[9]
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End point description:

SD-OCT was used to assess change in central horizontal ellipsoid width. The measurements were taken after dilation of the participant's pupil. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	47		
Units: microns				
arithmetic mean (standard deviation)				
Study Eye 1 (n=12, 45)	2346.0 (± 1511.67)	1951.2 (± 1223.26)		
Study Eye 2	2230.2 (± 1122.89)	1950.1 (± 1188.74)		

Statistical analyses

No statistical analyses for this end point

Primary: SD-OCT: Choroidal Thickness at Foveal Center at Month 12

End point title	SD-OCT: Choroidal Thickness at Foveal Center at Month 12 ^[10]
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End point description:

SD-OCT was used to assess change in choroidal thickness. The measurements were taken after dilation of the participant's pupil. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	52		
Units: microns				
arithmetic mean (standard deviation)				
Study Eye 1	185.5 (± 81.72)	174.2 (± 85.33)		
Study Eye 2	207.6 (± 85.89)	190.2 (± 87.40)		

Statistical analyses

No statistical analyses for this end point

Primary: SD-OCT: Square Root of Central Ellipsoid Area at Month 12

End point title	SD-OCT: Square Root of Central Ellipsoid Area at Month 12 ^[11]
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End point description:

SD-OCT was used to assess change in square root of central ellipsoid area. The measurements were taken after dilation of the participant's pupil. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	28		
Units: mm				
arithmetic mean (standard deviation)				
Study Eye 1 (n=7, 25)	1.6980 (\pm 0.62031)	1.6346 (\pm 0.55842)		
Study Eye 2	2.0331 (\pm 0.55575)	1.8468 (\pm 0.64385)		

Statistical analyses

No statistical analyses for this end point

Primary: AF: Mean Square Root of Total Area of Preserved AF at Month 12

End point title	AF: Mean Square Root of Total Area of Preserved AF at Month 12 ^[12]
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End point description:

AF was used to assess change in square root of total area of preserved AF. Here, negative values indicate decline in total area of preserved autofluorescence. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: mm				
arithmetic mean (standard deviation)				
Study Eye 1 (n=13, 50)	2.4358 (\pm 1.13836)	2.6149 (\pm 1.37197)		
Study Eye 2 (n=15, 49)	2.6214 (\pm 1.17348)	2.7550 (\pm 1.46149)		

Statistical analyses

No statistical analyses for this end point

Primary: Fundus Autofluorescence (AF): Mean Total Area of Preserved Autofluorescence at Month 12

End point title	Fundus Autofluorescence (AF): Mean Total Area of Preserved Autofluorescence at Month 12 ^[13]
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End point description:

AF was used to assess change in total area of preserved autofluorescence. Here, negative values indicate decline in total area of preserved autofluorescence. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified parameter.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: mm ²				
arithmetic mean (standard deviation)				
Study Eye 1 (n=13, 50)	7.130 (± 6.2326)	8.682 (± 9.8972)		
Study Eye 2 (n=15, 49)	8.157 (± 7.4969)	9.682 (± 11.0688)		

Statistical analyses

No statistical analyses for this end point

Primary: AF: Mean Distance From Foveal Center to Nearest Border of Preserved AF at Month 12

End point title	AF: Mean Distance From Foveal Center to Nearest Border of Preserved AF at Month 12 ^[14]
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End point description:

Fundus Autofluorescence was used to assess change in distance from foveal center to nearest border of preserved autofluorescence. Here, negative values indicate decline in total area of preserved autofluorescence. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: mm				
arithmetic mean (standard deviation)				
Study Eye 1	423.133 (± 559.1529)	370.245 (± 733.1618)		
Study Eye 2 (n=15, 52)	539.600 (± 602.6063)	525.212 (± 688.7141)		

Statistical analyses

No statistical analyses for this end point

Primary: Fundus Photography: Number of Participants With Retinal Pigment Epithelium (RPE) Hyperplasia as per Severity

End point title	Fundus Photography: Number of Participants With Retinal Pigment Epithelium (RPE) Hyperplasia as per Severity ^[15]
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End point description:

Number of participants with RPE hyperplasia are reported for severity grades: mild, moderate, severe. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	49		
Units: participants				
Mild: Study Eye 1	7	26		
Mild: Study Eye 2 (n=15, 48)	9	23		
Moderate: Study Eye 1	8	21		
Moderate: Study Eye 2 (n=15, 48)	6	23		
Severe: Study Eye 1	0	2		
Severe: Study Eye 2 (n=15, 48)	0	2		

Statistical analyses

No statistical analyses for this end point

Primary: Fundus Photography: Number of Participants With Retinal Arteriolar Narrowing as per Severity

End point title	Fundus Photography: Number of Participants With Retinal Arteriolar Narrowing as per Severity ^[16]
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End point description:

Number of participants with retinal arteriolar narrowing are reported for severity grades: mild, moderate, severe. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: participants				
Mild: Study Eye 1	13	37		
Mild: Study Eye 2 (n=15, 49)	12	36		
Moderate: Study Eye 1	1	10		
Moderate: Study Eye 2 (n=15, 49)	2	10		
Severe: Study Eye 1	0	0		
Severe: Study Eye 2 (n=15, 49)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Fundus Photography: Number of Participants With Retinal Vessel Sheathing as per Severity

End point title	Fundus Photography: Number of Participants With Retinal Vessel Sheathing as per Severity ^[17]
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End point description:

Number of participants with retinal vessel sheathing are reported for severity grades: mild, moderate, severe. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	49		
Units: participants				
Mild: Study Eye 1	0	0		
Mild: Study Eye 2 (n=15, 48)	0	0		
Moderate: Study Eye 1	0	0		
Moderate: Study Eye 2 (n=15, 48)	0	0		
Severe: Study Eye 1	0	0		
Severe: Study Eye 2 (n=15, 48)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Fundus Photography: Number of Participants With Optic Atrophy/Pallor as per Severity

End point title	Fundus Photography: Number of Participants With Optic Atrophy/Pallor as per Severity ^[18]
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End point description:

Number of participants with optic atrophy/pallor are reported for severity grades: mild, moderate, severe. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: participants				
Mild: Study Eye 1	0	0		
Mild: Study Eye 2 (n=15, 49)	0	0		
Moderate: Study Eye 1	0	0		
Moderate: Study Eye 2 (n=15, 49)	0	0		
Severe: Study Eye 1	0	0		
Severe: Study Eye 2 (n=15, 49)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Fundus Photography: Number of Participants With Optic Disc Swelling as per Severity

End point title	Fundus Photography: Number of Participants With Optic Disc Swelling as per Severity ^[19]
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End point description:

Number of participants with optic disc swelling are reported for severity grades: mild, moderate, severe. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: participants				
Mild: Study Eye 1	0	1		
Mild: Study Eye 2 (n=15, 49)	0	0		
Moderate: Study Eye 1	0	0		
Moderate: Study Eye 2 (n=15, 49)	0	0		
Severe: Study Eye 1	0	0		
Severe: Study Eye 2 (n=15, 49)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Microperimetry: Retinal Mean Sensitivity at Month 12

End point title	Microperimetry: Retinal Mean Sensitivity at Month 12 ^[20]
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End point description:

Microperimetry was conducted to assess retinal mean sensitivity within the macula. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: decibels (dB)				
arithmetic mean (standard deviation)				
Study Eye 1	4.05 (± 4.565)	5.93 (± 6.991)		
Study Eye 2	5.41 (± 5.239)	6.37 (± 6.720)		

Statistical analyses

No statistical analyses for this end point

Primary: Microperimetry: Bivariate Contour Ellipse Area 63% at Month 12

End point title	Microperimetry: Bivariate Contour Ellipse Area 63% at Month 12 ^[21]
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End point description:

Microperimetry was conducted to assess bivariate contour ellipse area 63%. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: square degrees (deg^2)				
arithmetic mean (standard deviation)				
Study Eye 1	7.91 (± 13.287)	2.09 (± 4.701)		
Study Eye 2	1.45 (± 1.874)	1.92 (± 5.510)		

Statistical analyses

No statistical analyses for this end point

Primary: Microperimetry: Fixation Losses (in Percentage) at Month 12

End point title	Microperimetry: Fixation Losses (in Percentage) at Month 12 ^[22]
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End point description:

Microperimetry was conducted to assess change in fixation losses (in percentage). All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number

of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	23		
Units: percentage (%)				
arithmetic mean (standard deviation)				
Study Eye 1	9.0 (± 12.45)	2.2 (± 7.20)		
Study Eye 2	4.0 (± 8.94)	5.0 (± 9.17)		

Statistical analyses

No statistical analyses for this end point

Primary: Microperimetry: Bivariate Contour Ellipse Area 95% at Month 12

End point title	Microperimetry: Bivariate Contour Ellipse Area 95% at Month 12 ^[23]
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End point description:

Microperimetry was conducted to assess bivariate contour ellipse area 95%. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: deg^2				
arithmetic mean (standard deviation)				
Study Eye 1	23.69 (± 39.857)	6.27 (± 14.106)		
Study Eye 2	4.35 (± 5.624)	5.76 (± 16.518)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With at Least one Treatment-Emergent Adverse Event (TEAE)

End point title	Percentage of Participants With at Least one Treatment-Emergent Adverse Event (TEAE) ^[24]
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End point description:

An AE is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug/surgical procedure, whether or not related to the investigational product or with the surgical procedure. TEAEs are defined as AEs starting on or after the day of the first surgery. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. The AEs data were collected and reported for unique participants instead of period-wise treated population.

End point type	Primary
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End point timeframe:

Day 0 (surgery) in period 1 up to last follow up visit in period 2 (approximately 2 years)

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	56		
Units: percentage of participants				
number (not applicable)	100	96.4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Vector Shedding Post-treatment at Month 3

End point title	Number of Participants With Vector Shedding Post-treatment at Month 3 ^[25]
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End point description:

Tears (for both eyes- oculus dexter [OD] and oculus sinister [OS]), blood, urine and saliva samples were collected and tested using an appropriate assay for evidence of vector shedding. Participants with positive result for vector shedding post treatment are reported. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified parameter.

End point type	Primary
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End point timeframe:

Baseline, at Month 3

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: participants				
Tears OD (n=47, 54)	0	0		
Tears OS (n=48, 55)	0	0		
Blood (n=47, 55)	0	0		
Saliva (n=48, 54)	0	0		
Urine (n=47, 56)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Anti-drug Antibodies Post-treatment at Month 12

End point title	Number of Participants With Anti-drug Antibodies Post-treatment at Month 12 ^[26]
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End point description:

Participants with antibodies to the REP-1 transgenic product are reported. The immunogenicity analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2 with baseline sample and at least one post-surgery sample evaluable for immunogenicity.

End point type	Primary
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End point timeframe:

Month 12

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	56		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Vital Signs: Change From Baseline in Blood Pressure at Month 12

End point title	Vital Signs: Change From Baseline in Blood Pressure at Month 12 ^[27]
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End point description:

Change from baseline in Systolic and diastolic blood pressures (SBP and DBP) [mmHg] were reported. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for

endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis at specified timepoint.

End point type	Primary
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End point timeframe:

Baseline, Month 12

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	22		
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic BP (SBP): Baseline	122.3 (± 14.73)	125.4 (± 11.52)		
SBP: Change at Month 12 (n=14, 22)	-7.2 (± 16.12)	-2.0 (± 10.65)		
Diastolic BP (DBP): Baseline	78.3 (± 9.56)	80.5 (± 6.91)		
DBP: Change at Month 12 (n=14, 22)	-1.0 (± 11.29)	-1.9 (± 9.60)		

Statistical analyses

No statistical analyses for this end point

Primary: Vital Signs: Change From Baseline in Pulse Rate at Month 12

End point title	Vital Signs: Change From Baseline in Pulse Rate at Month 12 ^[28]
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End point description:

Change from baseline in pulse rate (beats per minute) were reported. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis at specified timepoint.

End point type	Primary
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End point timeframe:

Baseline, Month 12

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned or performed for this endpoint.

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	22		
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline	69.8 (± 13.31)	71.5 (± 10.91)		
Change at Month 12 (n=14, 22)	6.7 (± 16.41)	0.9 (± 10.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BCVA as Measured by the ETDRS Chart

End point title	Change From Baseline in BCVA as Measured by the ETDRS Chart
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End point description:

BCVA was assessed for both eyes using the ETDRS VA chart. BCVA test should be performed prior to pupil dilation, and distance refraction should be carried out before BCVA is measured. Initially, letters are read at a distance of 4 meters from the chart. If <20 letters are read at 4 meters, testing at 1 meter should be performed. BCVA is reported as number of letters read correctly by the participant using the ETDRS Scale (ranging from 0 to 100 letters) in the study eyes. The lower the number of letters read correctly on the eye chart, the worse the vision (or VA). An increase in the number of letters read correctly means that vision has improved. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: letters				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	-8.6 (± 24.55)	-1.3 (± 7.77)		
Change at Month 12: Study Eye 2	2.2 (± 2.93)	-2.2 (± 8.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: AF: Change From Baseline in Total Area of Preserved Autofluorescence at Month 12

End point title	AF: Change From Baseline in Total Area of Preserved Autofluorescence at Month 12
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End point description:

AF was used to assess change in total area of preserved autofluorescence. Here negative values indicate decline in total area of preserved autofluorescence. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. Number of subjects analysed' indicates the number of subjects with data available for endpoint analysis. 'Number analysed (n)'

indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: mm ²				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1 (n=13,50)	-1.158 (± 1.3362)	-1.502 (± 1.9315)		
Change at Month 12: Study Eye 2 (n=15,49)	-0.772 (± 0.5381)	-1.313 (± 1.9967)		

Statistical analyses

No statistical analyses for this end point

Secondary: AF: Change From Baseline in Square Root of Total Area of Preserved AF at Month 12

End point title	AF: Change From Baseline in Square Root of Total Area of Preserved AF at Month 12
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End point description:

AF was used to assess change in square root of total area of preserved AF. Here negative values indicate decline in total area of preserved autofluorescence. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	50		
Units: mm				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye1 (n=13,50)	-0.1981 (± 0.13033)	-0.2197 (± 0.18111)		
Change at Month 12: Study Eye2 (n=15,49)	-0.1345 (± 0.04362)	-0.1736 (± 0.16090)		

Statistical analyses

No statistical analyses for this end point

Secondary: AF: Change From Baseline in Distance From Foveal Center to Nearest Border of Preserved AF at Month 12

End point title	AF: Change From Baseline in Distance From Foveal Center to Nearest Border of Preserved AF at Month 12
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End point description:

Fundus Autofluorescence was used to assess change in distance from foveal center to nearest border of preserved autofluorescence. Here negative values indicate decline in total area of preserved autofluorescence. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: mm				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	-160.000 (± 197.9094)	-94.321 (± 106.4964)		
Change at Month 12: Study Eye 2 (n=15,52)	-76.000 (± 71.9107)	-80.596 (± 135.5793)		

Statistical analyses

No statistical analyses for this end point

Secondary: SD-OCT: Change From Baseline in Foveal Subfield Thickness at Month 12

End point title	SD-OCT: Change From Baseline in Foveal Subfield Thickness at Month 12
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End point description:

SD-OCT was used to assess change in foveal subfield thickness. The measurements were taken after dilation of the participant's pupil. A negative change from baseline indicates decline in foveal subfield thickness. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: microns				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	1.7 (± 53.08)	-2.9 (± 12.02)		
Change at Month 12: Study Eye 2	-3.5 (± 7.40)	-5.7 (± 23.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: SD-OCT: Change From Baseline in Total Macular Volume at Month 12

End point title	SD-OCT: Change From Baseline in Total Macular Volume at Month 12
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End point description:

SD-OCT was used to assess change in total macular volume. The measurements were taken after dilation of the participant's pupil. A negative change from baseline indicates decline in total macular volume. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: mm ³				
arithmetic mean (standard deviation)				
Change at Month12:StudyEye1(n=14,53)	-0.201 (± 0.2275)	-0.188 (± 0.1400)		
Change at Month 12: Study Eye 2	-0.093 (± 0.1344)	-0.233 (± 0.3969)		

Statistical analyses

No statistical analyses for this end point

Secondary: SD-OCT: Change From Baseline in the Central Horizontal Ellipsoid Width at Month 12

End point title	SD-OCT: Change From Baseline in the Central Horizontal Ellipsoid Width at Month 12
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End point description:

SD-OCT was used to assess change in central horizontal ellipsoid width. The measurements were taken after dilation of the participant's pupil. A negative change from baseline indicates decline in central horizontal ellipsoid width. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	44		
Units: microns				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1 (n=12,44)	-156.8 (\pm 185.66)	-161.5 (\pm 299.00)		
Change at Month 12: Study Eye 2 (n=14,43)	-217.5 (\pm 388.56)	-150.4 (\pm 360.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: SD-OCT: Change From Baseline in Central Ellipsoid Area at Month 12

End point title	SD-OCT: Change From Baseline in Central Ellipsoid Area at Month 12
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End point description:

SD-OCT was used to assess change in central ellipsoid area. The measurements were taken after dilation of the participant's pupil. A negative change from baseline indicates decline in central ellipsoid area. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	27		
Units: mm ²				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1 (n=6,23)	-0.408 (± 0.2184)	-0.452 (± 0.2776)		
Change at Month 12: Study Eye 2	-0.466 (± 0.3543)	-0.369 (± 0.3425)		

Statistical analyses

No statistical analyses for this end point

Secondary: SD-OCT: Change From Baseline in Square Root of Central Ellipsoid Area at Month 12

End point title	SD-OCT: Change From Baseline in Square Root of Central Ellipsoid Area at Month 12
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End point description:

SD-OCT was used to assess change in square root of central ellipsoid area. The measurements were taken after dilation of the participant's pupil. A negative change from baseline indicates decline in square root of central ellipsoid area. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis. 'Number analysed (n)' indicates the number of participants with data available for analysis of specified eye.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	27		
Units: mm				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1 (n=6,23)	-0.1348 (± 0.08110)	-0.1345 (± 0.06117)		
Change at Month 12: Study Eye 2	-0.1121 (± 0.08193)	-0.0944 (± 0.09347)		

Statistical analyses

No statistical analyses for this end point

Secondary: SD-OCT: Change From Baseline in the Choroidal Thickness at Foveal Center at Month 12

End point title	SD-OCT: Change From Baseline in the Choroidal Thickness at Foveal Center at Month 12
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End point description:

SD-OCT was used to assess change in choroidal thickness. The measurements were taken after dilation of the participant's pupil. A negative change from baseline indicates decline in choroidal thickness. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	56		
Units: microns				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	-12.9 (\pm 35.57)	-13.7 (\pm 30.73)		
Change at Month 12: Study Eye 2	-9.8 (\pm 23.73)	2.9 (\pm 23.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Microperimetry: Change From Baseline in Mean Retinal Sensitivity at Month 12

End point title	Microperimetry: Change From Baseline in Mean Retinal Sensitivity at Month 12
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End point description:

Microperimetry was conducted to assess change in mean retinal sensitivity within the macula. A negative change from baseline indicates decline in retinal sensitivity. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: dB				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	-0.79 (\pm 1.160)	-0.38 (\pm 1.931)		
Change at Month 12: Study Eye 2	0.15 (\pm 0.725)	-0.73 (\pm 1.435)		

Statistical analyses

No statistical analyses for this end point

Secondary: Microperimetry: Change From Baseline in Bivariate Contour Ellipse Area 63% at Month 12

End point title	Microperimetry: Change From Baseline in Bivariate Contour Ellipse Area 63% at Month 12
End point description:	
Microperimetry was conducted to assess change in bivariate contour ellipse area 63%. A negative change from baseline indicates decline in bivariate contour ellipse area 63%. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: deg^2				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	4.42 (\pm 14.383)	-0.22 (\pm 6.733)		
Change at Month 12: Study Eye 2	-0.02 (\pm 1.296)	0.63 (\pm 5.681)		

Statistical analyses

No statistical analyses for this end point

Secondary: Microperimetry: Change From Baseline in the Bivariate Contour Ellipse Area 95% at Month 12

End point title	Microperimetry: Change From Baseline in the Bivariate Contour
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End point description:

Microperimetry was conducted to assess change in bivariate contour ellipse area 95%. A negative change from baseline indicates decline in bivariate contour ellipse area 95%. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	53		
Units: deg ²				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	13.23 (± 43.125)	-0.66 (± 20.204)		
Change at Month 12: Study Eye 2	-0.09 (± 3.866)	1.90 (± 17.006)		

Statistical analyses

No statistical analyses for this end point

Secondary: Microperimetry: Change From Baseline in Fixation Losses (in Percentage) at Month 12

End point title	Microperimetry: Change From Baseline in Fixation Losses (in Percentage) at Month 12
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End point description:

Microperimetry was conducted to assess change in fixation losses (in percentage). A negative change from baseline indicates decline in fixation losses. All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. 'Number of subjects analysed' indicates the number of participants with data available for endpoint analysis.

End point type	Secondary
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End point timeframe:

Baseline, Month 12

End point values	Treatment Period 1: BIIB111	Treatment Period 2: BIIB111		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	14		
Units: percentage				
arithmetic mean (standard deviation)				
Change at Month 12: Study Eye 1	5.3 (± 13.60)	-4.5 (± 11.72)		
Change at Month 12: Study Eye 2	-6.3 (± 12.50)	2.8 (± 7.40)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 0 (surgery) in period 1 up to last follow up visit in period 2 (approximately 2 years)

Adverse event reporting additional description:

All Treated Subjects analysis set included all participants who completed the 'Day of Surgery' visit of Period 1 or 2. The AEs data were collected and reported for unique participants enrolled in the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Treatment Period 2: BIIB111
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Reporting group description:

After vitrectomy and retinal detachment in the study eye 2, participants received a single administration of BIIB111, 1 * 10¹¹ gp, as a sub-retinal injection on Day 0 (surgery day) of Period 2.

Reporting group title	Treatment Period 1: BIIB111
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Reporting group description:

After vitrectomy and retinal detachment in the study eye 1, participants received a single administration of BIIB111, 1 * 10¹¹ gp, as a sub-retinal injection on Day 0 (surgery day) of Period 1.

Serious adverse events	Treatment Period 2: BIIB111	Treatment Period 1: BIIB111	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 56 (14.29%)	12 / 60 (20.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Eye disorders			
Choroidal neovascularisation			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness unilateral			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Noninfective retinitis			
subjects affected / exposed	0 / 56 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Visual acuity reduced			
subjects affected / exposed	6 / 56 (10.71%)	10 / 60 (16.67%)	
occurrences causally related to treatment / all	3 / 7	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tractional retinal detachment			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye inflammation			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal degeneration			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depression			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment Period 2: BIIB111	Treatment Period 1: BIIB111	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 56 (94.64%)	59 / 60 (98.33%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	8 / 56 (14.29%)	6 / 60 (10.00%)	
occurrences (all)	15	8	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 56 (12.50%)	7 / 60 (11.67%)	
occurrences (all)	8	10	
Eye disorders			
Eye irritation			
subjects affected / exposed	9 / 56 (16.07%)	8 / 60 (13.33%)	
occurrences (all)	9	9	

Conjunctival hyperaemia		
subjects affected / exposed	6 / 56 (10.71%)	11 / 60 (18.33%)
occurrences (all)	9	11
Foreign body sensation in eyes		
subjects affected / exposed	10 / 56 (17.86%)	11 / 60 (18.33%)
occurrences (all)	10	12
Eye pain		
subjects affected / exposed	10 / 56 (17.86%)	9 / 60 (15.00%)
occurrences (all)	12	10
Anterior chamber cell		
subjects affected / exposed	32 / 56 (57.14%)	29 / 60 (48.33%)
occurrences (all)	37	35
Conjunctival haemorrhage		
subjects affected / exposed	36 / 56 (64.29%)	38 / 60 (63.33%)
occurrences (all)	38	38
Vitreous cells		
subjects affected / exposed	4 / 56 (7.14%)	7 / 60 (11.67%)
occurrences (all)	4	8
Vitritis		
subjects affected / exposed	8 / 56 (14.29%)	7 / 60 (11.67%)
occurrences (all)	17	10
Dry eye		
subjects affected / exposed	6 / 56 (10.71%)	2 / 60 (3.33%)
occurrences (all)	10	3
Anterior chamber flare		
subjects affected / exposed	4 / 56 (7.14%)	5 / 60 (8.33%)
occurrences (all)	4	5
Vision blurred		
subjects affected / exposed	6 / 56 (10.71%)	4 / 60 (6.67%)
occurrences (all)	8	4
Conjunctival oedema		
subjects affected / exposed	3 / 56 (5.36%)	6 / 60 (10.00%)
occurrences (all)	3	6
Visual impairment		
subjects affected / exposed	4 / 56 (7.14%)	9 / 60 (15.00%)
occurrences (all)	5	10

Ocular discomfort		
subjects affected / exposed	7 / 56 (12.50%)	3 / 60 (5.00%)
occurrences (all)	9	4
Metamorphopsia		
subjects affected / exposed	5 / 56 (8.93%)	2 / 60 (3.33%)
occurrences (all)	6	2
Photopsia		
subjects affected / exposed	6 / 56 (10.71%)	1 / 60 (1.67%)
occurrences (all)	10	4
Visual acuity reduced		
subjects affected / exposed	3 / 56 (5.36%)	4 / 60 (6.67%)
occurrences (all)	3	4
Cataract		
subjects affected / exposed	4 / 56 (7.14%)	1 / 60 (1.67%)
occurrences (all)	7	2
Cystoid macular oedema		
subjects affected / exposed	4 / 56 (7.14%)	1 / 60 (1.67%)
occurrences (all)	5	2
Eye pruritus		
subjects affected / exposed	3 / 56 (5.36%)	3 / 60 (5.00%)
occurrences (all)	3	3
Subretinal fluid		
subjects affected / exposed	2 / 56 (3.57%)	3 / 60 (5.00%)
occurrences (all)	3	3
Vitreous floaters		
subjects affected / exposed	4 / 56 (7.14%)	1 / 60 (1.67%)
occurrences (all)	6	1
Eyelid ptosis		
subjects affected / exposed	4 / 56 (7.14%)	1 / 60 (1.67%)
occurrences (all)	4	1
Ocular hypertension		
subjects affected / exposed	2 / 56 (3.57%)	3 / 60 (5.00%)
occurrences (all)	2	4
Cataract subcapsular		
subjects affected / exposed	3 / 56 (5.36%)	1 / 60 (1.67%)
occurrences (all)	4	2

Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 60 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 6	8 / 60 (13.33%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2018	Amendment 1 states: • New text added to clarify time period between surgeries and requirement for an assessment of overall ocular health and function before scheduling of second eye. • Added text to clarify that if the post-operatively severe ocular inflammation is present, the participant would be terminated from the trial, and that any post-operative complication or poor visual outcome prevents the second eye from continuing to surgery. • Details of the vitrectomy procedure have been added for clarification. Emergency contact information has been added. • New Section added for additional safety gating and stopping criteria. Immunogenicity testing has been specified. • Steroid therapy in the perioperative period was clarified for when surgeries are temporally close.
03 February 2019	Amendment 2 states: • Sample size was increased from 15 to 60. • Specific language was added regarding allocation of 60 participants into 3 surgery windows of varying length, to provide the broadest safety profile available on participants treated with short, medium, and long time periods between surgeries. • Corticosteroid regimen was revised to clarify administration required with bilateral treatment performed with very short windows between surgeries. • Visual acuity inclusion criterion was revised to allow for eligibility of participants with more significant visual impairment. • New inclusion criterion has been added mandating that participants who enter this study from an antecedent study must have biological samples available to complete an adequate immunogenicity profile • Added benefit-risk assessment section to the Introduction, that outlines the expected risks of AAV2-REP1 treatment to include visual acuity loss post-treatment. • Definition of vision loss as a serious adverse event was clarified.
29 October 2019	Amendment 3 states: • Visit windows was updated for Visit 3 (Day 3 + 2 days, post-operative follow-up visit) and Visit 4 (Day 7 -1/+2 day) to decrease patient burden and minimize weekend post-operative follow-ups. • Additional information was added to better define serious adverse events. • Updated the Reference Safety Information and the Investigator's Brochure based on the new data derived from the STAR study.
30 April 2020	Amendment 4 states: • Added text to include study eye selection and eligibility for surgery as defined by the Patient Eligibility Review Committee.
11 November 2020	Amendment 5 states: • Added the maximum dose of 80 mg daily of corticosteroid to the corticosteroid regimen. Patient Eligibility Review Committee was added to the Synopsis Exclusion Criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported