Clinical trial results:
A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1) [STAR]

Summary

EudraCT number	2015-003958-41
Trial protocol	DE FI DK NL
Global end of trial date	01 December 2020

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	273CH301 (NSR-REP-01)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03496012
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, 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	01 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 December 2020
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 efficacy and safety of a single sub-retinal injection of BIIB111 in subjects with choroideremia (CHM).

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative, as applicable, prior to evaluations performed for eligibility. Subjects or the subject'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:

Subjects who received BIIB111 (timrepigene emparvovec) were given a 21-day course of oral corticosteroid (e.g., prednisolone/prednisone). The schedule was as follows: 1 milligram per kilogram/day (mg/kg/day) prednisolone/prednisone for a total of 10 days, (beginning 2 days before the vector injection, on the day of injection, and then for 7 days), followed by 0.5 mg/kg/day for 7 days, then 0.25 mg/kg/day for 2 days and 0.125 mg/kg/day for 2 days (21 days in total). Weight captured at Visit 1 (Screening/Baseline) was used to calculate the required dose during the 21-day course, and all doses were rounded to the nearest 1 mg.

Evidence for comparator: -

Actual start date of recruitment	11 December 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	Germany: 32
Country: Number of subjects enrolled	United States: 74
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Denmark: 2
Worldwide total number of subjects	169
EEA total number of subjects	74

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)	148
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at the investigative sites in the United States, Germany, Finland, France, the United Kingdom, Canada, Netherlands, and Denmark from 11 December 2017 to 01 December 2020.

Pre-assignment

Screening details:

A total of 169 subjects with Choroideremia were randomized in the study (66 subjects in Untreated Control Group; 34 subjects in BIIB111 Low Dose group and 69 subjects in BIIB111 High Dose group). Of which, 161 subjects completed the study.

Period 1

Period 1 title	Overall Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Subjects were dose blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Untreated Control Group

Arm description:

Subjects received no sham surgery or study medication to allow for a controlled comparison.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	BIIB111 Low Dose

Arm description:

Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of low dose (1.0 × 10^10 genome particle [gp]) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).

Arm type	Experimental
Investigational medicinal product name	Timrepigene Emparvovec
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.

Arm title	BIIB111 High Dose

Arm description:

Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of high dose (1.0 × 10^11 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).

Arm type	Experimental
Investigational medicinal product name	Timrepigene Emparvovec
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	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose
Started	66	34	69
Completed	62	34	65
Not completed	4	0	4
Reason Not Specified	2	-	1
Serious adverse event	-	-	1
Withdrawal by subject	2	-	2

Period 2

Period 2 title	Intent to Treat (ITT) Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Subjects were dose blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Untreated Control Group

Arm description:

Subjects received no sham surgery or study medication to allow for a controlled comparison.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	BIIB111 Low Dose

Arm description:

Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of low dose (1.0 × 10^10 genome particle [gp]) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).

Arm type	Experimental
Investigational medicinal product name	Timrepigene Emparvovec
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.

Arm title	BIIB111 High Dose

Arm description:

Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of high dose (1.0 × 10^11 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).

Arm type	Experimental
Investigational medicinal product name	Timrepigene Emparvovec
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.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline data is reported for ITT population so ITT period is selected as baseline period.

Number of subjects in period 2[2]	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose
Started	62	34	65
Completed	62	34	65

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline data is reported for ITT population but not randomized population.

Baseline characteristics

Reporting groups	
Reporting group title	Untreated Control Group
Reporting group description:	
Subjects received no sham surgery or study medication to allow for a controlled comparison.	
Reporting group title	BIIB111 Low Dose
Reporting group description:	
Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of low dose (1.0 × 10^10 genome particle [gp]) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).	
Reporting group title	BIIB111 High Dose
Reporting group description:	
Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of high dose (1.0 × 10^11 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).	

Reporting group values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose
Number of subjects	62	34	65
Age Categorical Units: subjects			
Age Continuous Units: years			
arithmetic mean	49.1	49.8	47.5
standard deviation	± 13.54	± 12.62	± 12.91
Gender Categorical Units: subjects			
Female	0	0	0
Male	62	34	65
Race Units: Subjects			
Asian	0	0	1
American Indian or Alaska Native	1	0	0
Black or African American	1	0	0
White	52	30	59
Other	1	0	0
Not Reported	7	4	5
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	4
Not Hispanic or Latino	49	26	54
Not Reported	10	7	7

Reporting group values	Total		
Number of subjects	161		
Age Categorical Units: subjects			

Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender Categorical Units: subjects			
Female	0		
Male	161		
Race Units: Subjects			
Asian	1		
American Indian or Alaska Native	1		
Black or African American	1		
White	141		
Other	1		
Not Reported	16		
Ethnicity Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	129		
Not Reported	24		

End points

End points reporting groups

Reporting group title	Untreated Control Group
Reporting group description:	
Subjects received no sham surgery or study medication to allow for a controlled comparison.	

Reporting group title	BIIB111 Low Dose
Reporting group description:	
Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of low dose (1.0 × 10^10 genome particle [gp]) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).	

Reporting group title	BIIB111 High Dose
Reporting group description:	
Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of high dose (1.0 × 10^11 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).	

Reporting group title	Untreated Control Group
Reporting group description:	
Subjects received no sham surgery or study medication to allow for a controlled comparison.	

Reporting group title	BIIB111 Low Dose
Reporting group description:	
Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of low dose (1.0 × 10^10 genome particle [gp]) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).	

Reporting group title	BIIB111 High Dose
Reporting group description:	
Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of high dose (1.0 × 10^11 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).	

Primary: Percentage of Subjects with a ≥15 -Letter Improvement from Baseline in Best Corrected Visual Acuity (BCVA) at Month 12 as Measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart

End point title	Percentage of Subjects with a ≥15 -Letter Improvement from Baseline in Best Corrected Visual Acuity (BCVA) at Month 12 as Measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart
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 to be reported as number of letters read correctly by the subject using the ETDRS Scale (ranging from 0 to 100 letters) in the study and fellow 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. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement.	

End point type	Primary
End point timeframe:	
Month 12	

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	34	65	
Units: percentage of subjects				
number (confidence interval 95%)				
Study Eye	0 (0 to 5.8)	2.9 (0.1 to 15.3)	4.6 (1.0 to 12.9)	
Fellow Eye	0 (0 to 5.8)	0 (0 to 10.3)	3.1 (0.4 to 10.7)	

Statistical analyses

Statistical analysis title	Study Eyes of Control Group vs BIIB111 Low Dose
Comparison groups	Untreated Control Group v BIIB111 Low Dose
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.354
Method	Fisher exact
Parameter estimate	Difference in Proportions
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	15

Statistical analysis title	Study Eyes of Control Group vs BIIB111 High Dose
Comparison groups	Untreated Control Group v BIIB111 High Dose
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245
Method	Fisher exact
Parameter estimate	Difference in proportions
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	12.8

Secondary: Change from Baseline in BCVA at Month 12 Measured by the ETDRS Chart

End point title	Change from Baseline in BCVA at Month 12 Measured by the ETDRS Chart

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 to be reported as number of letters read correctly by the subject using the ETDRS Scale (ranging from 0 to 100 letters) in the study and fellow 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. ITT Population included all randomized participants who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number Analyzed' signifies number of participants analyzed at the specified timepoint in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	34	65	
Units: letters				
least squares mean (confidence interval 95%)				
Change From Baseline at Month 12: Study Eye	-2.3 (-5.31 to 0.61)	-1.5 (-5.47 to 2.50)	-0.3 (-3.18 to 2.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a ≥10 -Letter Improvement from Baseline in BCVA at Month 12 Measured by the ETDRS Chart

End point title	Percentage of Subjects with a ≥10 -Letter Improvement from Baseline in BCVA at Month 12 Measured by the ETDRS Chart

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 to be reported as number of letters read correctly by the subject using the ETDRS Scale (ranging from 0 to 100 letters) in the study and fellow 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. ITT Population included all randomized participants who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement.

End point type	Secondary

End point timeframe:

Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	34	65	
Units: percentage of subjects				
number (confidence interval 95%)				
Study Eye	1.6 (0.0 to 8.7)	17.6 (6.8 to 34.5)	13.8 (6.5 to 24.7)	
Fellow Eye	0 (0.0 to 5.8)	8.8 (1.9 to 23.7)	6.2 (1.7 to 15.0)	

Statistical analyses

Statistical analysis title	Study Eyes of Control Group vs BIIB111 Low Dose
Comparison groups	Untreated Control Group v BIIB111 Low Dose
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in proportions
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	32.2

Statistical analysis title	Study Eyes of Control Group vs BIIB111 High Dose
Comparison groups	Untreated Control Group v BIIB111 High Dose
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in proportions
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	23

Secondary: Percentage of Subjects with No Decrease from Baseline in BCVA or a Decrease from Baseline in BCVA of <5 ETDRS Letters at Month 12 Measured by the EDRS Chart

End point title	Percentage of Subjects with No Decrease from Baseline in BCVA or a Decrease from Baseline in BCVA of <5 ETDRS Letters at Month 12 Measured by the EDRS Chart

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 to be reported as number of letters read correctly by the subject using the ETDRS Scale (ranging from 0 to 100 letters) in the study and fellow 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. ITT Population included all randomized participants who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement.

End point type	Secondary

End point timeframe:

Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	34	65	
Units: percentage of subjects				
number (confidence interval 95%)				
Study Eye	67.7 (54.7 to 79.1)	70.6 (52.5 to 84.9)	83.1 (71.7 to 91.2)	
Fellow Eye	75.8 (63.3 to 85.8)	85.3 (68.9 to 95.0)	90.8 (81.0 to 96.5)	

Statistical analyses

Statistical analysis title	Study Eyes of Control Group vs BIIB111 Low Dose
Comparison groups	Untreated Control Group v BIIB111 Low Dose
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in proportions
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	21

Statistical analysis title	Study Eyes of Control Group vs BIIB111 High Dose
Comparison groups	Untreated Control Group v BIIB111 High Dose

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in proportions
Point estimate	15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	30.1

Secondary: Change from Baseline in BCVA at Months 4 and 8 Measured by the ETDRS Chart

End point title	Change from Baseline in BCVA at Months 4 and 8 Measured by the ETDRS Chart

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 to be reported as number of letters read correctly by the subject using the ETDRS Scale (ranging from 0 to 100 letters) in the study and fellow 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. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. Here n=number of subjects analyzed at the specified timepoint in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Months 4 and 8

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	34	65	
Units: letters				
arithmetic mean (standard deviation)				
Baseline: Study Eye	60.4 (± 8.66)	61.8 (± 8.10)	58.7 (± 8.86)	
Baseline: Fellow Eye	59.8 (± 23.34)	65.3 (± 20.95)	62.5 (± 20.47)	
Month 4: Study Eye (n=61, 34, 65)	0.2 (± 4.34)	-0.4 (± 14.16)	0.6 (± 11.11)	
Month 4: Fellow Eye (n=61, 34, 64)	-1.1 (± 8.45)	0.9 (± 6.67)	2.0 (± 6.63)	
Month 8: Study Eye (n=61, 34, 65)	-0.8 (± 4.93)	-1.1 (± 13.13)	0.1 (± 11.71)	
Month 8: Fellow Eye (n=61, 34, 64)	-0.4 (± 8.31)	1.9 (± 7.06)	1.6 (± 5.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Area of Preserved Autofluorescence (AF) at Month 12

End point title	Change from Baseline in Total Area of Preserved Autofluorescence (AF) at Month 12

End point description:

Fundus Autofluoroscence was used to assess change in total area of preserved autofluoroscence. A negative change from baseline indicate decline in total area of preserved autofluoroscence. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	34	63	
Units: square millimetres (mm^2)				
least squares mean (standard error)	-0.3872 (± 0.0389)	-0.5413 (± 0.0501)	-0.5136 (± 0.0371)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Fundus Autofluoroscence was used to assess change in distance from foveal center (FC) to nearest border of preserved autofluoroscence. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	34	63	
Units: micrometres (µm)				
least squares mean (standard error)	21.7796 (± 9.6234)	23.6171 (± 12.3765)	21.1660 (± 9.1863)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Foveal Subfield Thickness Using Spectral Domain Optical Coherence Tomography (SD-OCT) at Month 12

End point title	Change from Baseline in the Foveal Subfield Thickness Using Spectral Domain Optical Coherence Tomography (SD-OCT) at Month 12

End point description:

SD-OCT was used to assess change in foveal subfield thickness. The measurements were taken after dilation of the subject's pupil. A negative change from baseline indicates decline in foveal subfield thickness. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	34	64	
Units: µm				
least squares mean (standard error)	-6.3152 (± 2.7779)	-19.8654 (± 3.6998)	-15.7993 (± 2.7233)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Total Macular Volume Using SD-OCT at Month 12

End point title	Change from Baseline in the Total Macular Volume Using SD-OCT at Month 12

End point description:

SD-OCT was used to assess change in total macular volume. The measurements were taken after dilation of the subject's pupil. A negative change from baseline indicates decline in total macular volume. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	34	64	
Units: cubic millimetres (mm^3)				
least squares mean (standard error)	-0.0895 (± 0.0485)	-0.2876 (± 0.0646)	-0.2088 (± 0.0476)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in the Central Horizontal Ellipsoid Width Using SD-OCT at Month 12

End point description:

SD-OCT was used to assess change in central horizontal ellipsoid width. The measurements were taken after dilation of the subject's pupil. A negative change from baseline indicates decline in central horizontal ellipsoid width. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	32	60	
Units: µm				
least squares mean (standard error)	-81.9178 (± 20.6192)	-116.3811 (± 27.8213)	-170.7214 (± 20.4062)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Central Ellipsoid Area Using SD-OCT at Month 12

End point title	Change from Baseline in the Central Ellipsoid Area Using SD-OCT at Month 12

End point description:

SD-OCT was used to assess change in central ellipsoid area. The measurements were taken after dilation of the subject's pupil. A negative change from baseline indicates decline in central ellipsoid area. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	18	44	
Units: mm^2				
least squares mean (standard error)	-0.2382 (± 0.0364)	-0.4229 (± 0.0527)	-0.3440 (± 0.0332)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Choroidal Thickness Using SD-OCT at Month 12

End point title	Change from Baseline in the Choroidal Thickness Using SD-OCT at Month 12

End point description:

SD-OCT was used to assess change in choroidal thickness. The measurements were taken after dilation of the subject's pupil. A negative change from baseline indicates decline in choroidal thickness. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	34	64	
Units: µm				
least squares mean (standard error)	-5.4897 (± 2.1873)	-7.9579 (± 2.9207)	-4.6371 (± 2.1446)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Mean Retinal Sensitivity Microperimetry Variable at Month 12

End point title	Change from Baseline in the Mean Retinal Sensitivity Microperimetry Variable at Month 12

End point description:

Microperimetry was used to assess change in mean retinal sensitivity. A negative change from baseline indicates decline in retinal sensitivity. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	34	61	
Units: decibels (dB)				
least squares mean (standard error)	-0.3443 (± 0.1134)	-0.2965 (± 0.1478)	-0.5015 (± 0.1112)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Bivariate Contour Ellipse Area 63% Microperimetry Variable at Month 12

End point title	Change from Baseline in the Bivariate Contour Ellipse Area 63% Microperimetry Variable at Month 12

End point description:

Microperimetry was used to assess change in bivariate contour ellipse area 63%. A negative change from baseline indicates decline in bivariate contour ellipse area 63%. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	34	61	
Units: square degree (deg^2)				
least squares mean (standard error)	-3.2161 (± 1.2623)	-3.3771 (± 1.6405)	-2.5555 (± 1.2403)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in the Bivariate Contour Ellipse Area 95% Microperimetry Variable at Month 12

End point description:

Microperimetry was used to assess change in bivariate contour ellipse area 95%. A negative change from baseline indicates decline in bivariate contour ellipse area 95%. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	34	61	
Units: deg^2				
least squares mean (standard error)	-10.1986 (± 4.1004)	-14.6926 (± 5.3134)	-11.6863 (± 4.0207)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Contrast Sensitivity Score at Month 12

End point title	Change from Baseline in Contrast Sensitivity Score at Month 12

End point description:

Change in contrast sensitivity was assessed by Pelli-Robson chart which uses a single large letter size (20/60 optotype), with contrast varying across groups of letters (6 per line), whose contrast varies from

high to low. Subjects read letters, starting with highest contrast, until they are unable to read 2 or 3 letters in a single group. Score is assigned based on contrast of last group in which 2 or 3 letters were correctly read. Score is a measure of subject`s log contrast sensitivity ranging from 0-2.25 (0 is no letters read and 2.25 is all letters read). Total CS score=[(total letters correct-3) x 0.05]. A negative change and a positive change from baseline indicates a worsening and an improvement in contrast sensitivity respectively. ITT Population=all randomized subjects who received study treatment (phone call for untreated control group) and have at least 1 post-treatment BCVA measurement. 'Number of Subjects Analyzed'=number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	34	65	
Units: score on a scale				
least squares mean (standard error)	-0.0595 (± 0.0315)	-0.0130 (± 0.0417)	-0.0386 (± 0.0304)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Colour Vision Total Error Score at Month 12

End point title	Change from Baseline in Colour Vision Total Error Score at Month 12

End point description:

Colour vision total error scores were assessed on the Farnsworth Munsell 100 Hue Sort Test. Farnsworth Munsell 100 Hue Test requires placing 100 colour palettes in the correct order based upon colour hue. Scores are determined by the frequency and severity of any displacement in the correct order. One error equates to one misplaced hue, by one step or position. An error score of 0 indicates no errors in ordering the hues while error score greater than 500 indicates virtually no color discrimination. A Total Error Score of 0 to 128 could be seen in a normal population. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	28	51	
Units: score on a scale				
least squares mean (standard error)	35.0003 (± 23.5973)	43.5915 (± 31.7720)	54.3777 (± 24.0358)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Reading Speed Test at Month 12

End point title	Change from Baseline in Reading Speed Test at Month 12

End point description:

The reading speed was calculated using the following formula: [number of words in the text - number of misread words] / reading time x 60. The number of misread words and reading time is collected. A negative change from baseline indicates decline in reading speed. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	12	27	
Units: words per minute				
least squares mean (standard error)	-149.5590 (± 10.9857)	-122.1333 (± 14.3276)	-127.4706 (± 9.9110)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the 25-Item Visual Function Questionnaire (VFQ-25) Composite Scores at Month 12

End point title	Change from Baseline in the 25-Item Visual Function Questionnaire (VFQ-25) Composite Scores at Month 12

End point description:

VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. A score of 0 represents the worst outcome and 100 represents the best outcome. A negative change from baseline indicates decline in VFQ-25 score. ITT Population included all randomized subjects who received the study treatment (or the phone call for those in the untreated control group) and have at least one post-treatment BCVA measurement. 'Number of Subjects Analyzed' signifies number of subjects analyzed in this outcome measure.

End point type	Secondary

End point timeframe:
Baseline, Month 12

End point values	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	34	63	
Units: score on a scale				
least squares mean (standard error)	-2.6971 (± 1.2786)	1.7236 (± 1.6624)	0.7964 (± 1.2308)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Signing of Informed Consent through End of Study (Up to 12 months)

Adverse event reporting additional description:

Safety population included all randomized subjects who either received study treatment BIIB111 (timrepigene emparvovec) or a post-randomization study visit (control group). Subjects were analyzed according to their actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Untreated Control Group

Reporting group description:

Subjects received no sham surgery or study medication to allow for a controlled comparison.

Reporting group title	BIIB111 Low Dose

Reporting group description:

Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of low dose (1.0 × 10^10 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).

Reporting group title	BIIB111 High Dose

Reporting group description:

Followed by vitrectomy and retinal detachment in the study eye, subjects received a single administration of high dose (1.0 × 10^11 gp) BIIB111 (timrepigene emparvovec) by sub-retinal injection on Day 0 (surgery day).

Serious adverse events	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 65 (15.38%)	9 / 34 (26.47%)	11 / 65 (16.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			

subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heterophoria			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	1 / 65 (1.54%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Noninfective retinitis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery embolism			
subjects affected / exposed	1 / 65 (1.54%)	0 / 34 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vascular occlusion			

subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	8 / 65 (12.31%)	5 / 34 (14.71%)	5 / 65 (7.69%)
occurrences causally related to treatment / all	0 / 8	5 / 6	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 34 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Covid-19 pneumonia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 34 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 34 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Untreated Control Group	BIIB111 Low Dose	BIIB111 High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 65 (13.85%)	30 / 34 (88.24%)	54 / 65 (83.08%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	6 / 65 (9.23%)
occurrences (all)	0	1	8
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Ocular procedural complication			
subjects affected / exposed	0 / 65 (0.00%)	1 / 34 (2.94%)	5 / 65 (7.69%)
occurrences (all)	0	1	5
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 65 (0.00%)	3 / 34 (8.82%)	7 / 65 (10.77%)
occurrences (all)	0	4	8
Eye disorders			
Anterior chamber cell			
subjects affected / exposed	0 / 65 (0.00%)	14 / 34 (41.18%)	24 / 65 (36.92%)
occurrences (all)	0	16	25
Anterior chamber flare			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	4 / 65 (6.15%)
occurrences (all)	0	2	5
Blepharitis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Cataract			
subjects affected / exposed	3 / 65 (4.62%)	3 / 34 (8.82%)	9 / 65 (13.85%)
occurrences (all)	3	3	12
Cataract subcapsular			
subjects affected / exposed	0 / 65 (0.00%)	4 / 34 (11.76%)	4 / 65 (6.15%)
occurrences (all)	0	5	4
Conjunctival haemorrhage			
subjects affected / exposed	0 / 65 (0.00%)	13 / 34 (38.24%)	26 / 65 (40.00%)
occurrences (all)	0	14	26
Conjunctival hyperaemia			
subjects affected / exposed	0 / 65 (0.00%)	4 / 34 (11.76%)	7 / 65 (10.77%)
occurrences (all)	0	5	8
Eye irritation			
subjects affected / exposed	0 / 65 (0.00%)	5 / 34 (14.71%)	8 / 65 (12.31%)
occurrences (all)	0	6	8
Eye pain			
subjects affected / exposed	0 / 65 (0.00%)	6 / 34 (17.65%)	11 / 65 (16.92%)
occurrences (all)	0	7	12
Foreign body sensation in eyes			
subjects affected / exposed	0 / 65 (0.00%)	3 / 34 (8.82%)	9 / 65 (13.85%)
occurrences (all)	0	3	9
Glare			

subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Low luminance best-corrected visual acuity decreased			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	7 / 65 (10.77%)
occurrences (all)	0	2	7
Ocular discomfort			
subjects affected / exposed	0 / 65 (0.00%)	0 / 34 (0.00%)	6 / 65 (9.23%)
occurrences (all)	0	0	6
Ocular hyperaemia			
subjects affected / exposed	0 / 65 (0.00%)	4 / 34 (11.76%)	7 / 65 (10.77%)
occurrences (all)	0	4	8
Retinal haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	3 / 34 (8.82%)	2 / 65 (3.08%)
occurrences (all)	1	3	2
Vision blurred			
subjects affected / exposed	0 / 65 (0.00%)	3 / 34 (8.82%)	1 / 65 (1.54%)
occurrences (all)	0	3	1
Vitreal cells			
subjects affected / exposed	0 / 65 (0.00%)	3 / 34 (8.82%)	4 / 65 (6.15%)
occurrences (all)	0	3	4
Vitritis			
subjects affected / exposed	0 / 65 (0.00%)	10 / 34 (29.41%)	16 / 65 (24.62%)
occurrences (all)	0	10	19
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 65 (1.54%)	2 / 34 (5.88%)	0 / 65 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Impetigo			

subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	0 / 65 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	4 / 65 (6.15%)	3 / 34 (8.82%)	6 / 65 (9.23%)
occurrences (all)	4	3	8
Pneumonia			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	2 / 65 (3.08%)
occurrences (all)	0	2	2
Sinusitis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 34 (5.88%)	1 / 65 (1.54%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2015	Removed treatment of the timrepigene emparvovec fellow eye in 4 to 6 subjects. Removed requirement for conducting the International Speed Reading Test in countries where validated translations were not available.
26 February 2016	Changed volume of timrepigene emparvovec subretinal injection from 0.05 mL to 0.1 mL (containing 1 x 1011 vg). Changed VA inclusion criterion for the study eye, from BCVA of 34 to 78 letters to a BCVA of 34 to 73. Removed randomization method for selection of the 'Study eye', and replaced with a requirement for the investigator to use clinical judgment (in collaboration with the subject) to select the 'Study eye', which was generally the worse eye. Clarification of management of Screening Identification and inclusion of Screen Failure data. Removed reference to an Interactive Voice/Web Response System for purposes of treatment randomization. Included prednisone (in addition to prednisolone) as the corticosteroid of choice in the 21-day perioperative period. Added requirement that subjects must have had a genetically confirmed diagnosis of CHM prior to the Screening Visit (Visit 1). Visit windows for Visits 7, 8, and 9 decreased from ± 21 days to ± 14 days.
01 August 2017	Updated title to reflect changes in study design. Changed choice of study control and randomization to a parallel, untreated control 3-arm study design (high-dose, low-dose, untreated-control). Increased sample size from 100 to 140 subjects. Increased the ETDRS BCVA letter improvement from 10 to 15 for the primary endpoint. Amended the key secondary endpoint to utilize Study NSR-CHM-OS1 (NIGHT study) as an historical control.
15 March 2019	Changes to statistical aspects of the study: Increased the sample size from 140 to 160 subjects; Changed the secondary endpoint from a historical comparison to prospective within-study assessments. Risk-benefit assessment was added to clarify vision loss as a known possible AE, therefore precluding it from SUSAR reporting; definition of SAEs associated with vision loss was also clarified. Other changes involved defining Day 0 for untreated subjects to assure that the duration of follow-up was equal for both treated and untreated subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported