VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
Version 1	31JAN2020	Original version
Version 2	03MAR2022	Removed planned analyses on Fixation Location due to data availability Removed planned analyses on time to resolution of AEs to keep consistency with other studies in the BIIB111 program. Changed planned analyses on microperimetry to exploratory to be performed as post-hoc analyses if needed Changed efficacy analyses to use observed case method as the main analyses. Added additional supportive analyses of BCVA-related endpoints, including LOCF imputation Adjusted subgroups for subgroup analyses Added summary on impact of COVID-19, and on protocol deviations Added details for immunogenicity and vector shedding Removed lists of table figure listing Removed inflammation related MedDRA Preferred Terms Provided additional clarification and information on definitions

Statistical Analysis Plan

GEMINI Study

PROTOCOL: **273CH203 / NSR-REP-02 (Timrepigene emparvovec)**
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) (GEMINI)

INDICATION: Choroideremia

STUDY PHASE: 2

EUDRACT NUMBER: 2017-002395-75

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SPONSOR: Biogen
225 Binney Street
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SAP for GEMINI Protocol Version	Amendment 3, Version 4
Document Status:	Final Version 2.0
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Statistical Analysis Plan

GEMINI Study

SPONSOR APPROVAL SIGNATURES

PROTOCOL: **273CH203 / NSR-REP-02 (Timrepigene emparvovec)**
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) (GEMINI)

Date 03MAR2022

The persons listed below are authorized to sign the Statistical Analysis Plan for this study, 273CH203 GEMINI, on behalf of Biogen / NightstaRx Ltd.

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Table of Contents

List of Tables

List of Figures

Abbreviations

AAV	adeno-associated viral vector
ADA	anti-drug antibodies
AE	adverse event
ATC	anatomical therapeutic chemical
AF	autofluorescence
BCVA	best corrected visual acuity
BIIB111	timrepigene emparvovec
CHM	choroideremia
CI	confidence interval
CM	concomitant medication
CSR	clinical study report
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ERM	epiretinal membrane
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FC	foveal center
IOP	intraocular pressure
LOCF	last observation carried forward
LOCS	lens opacities classification system
MAIA	Macular Integrity Assessment
MedDRA	Medical Dictionary for Regulatory Activities
MH	macular hole
Nabs	neutralizing timrepigene emparvovec antibodies
OD	oculus dextrus (right eye)
OU	oculus uterque (both eyes)
OS	oculus sinister (left eye)
P05	fifth percentile
P95	ninety fifth percentile
PT	preferred term
Q1	first quartile
Q3	third quartile
REP1	rab escort protein 1
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SE1	study eye 1
SE2	study eye 2
SFU	spot forming units
SOC	system organ class
SRF	subretinal fluid

TEAE	treatment-emergent adverse event
USAN	United States adopted name
vg	vector genomes
VMT	vitreomacular traction
WHODD	World Health Organisation drug dictionary

1 Introduction

This document presents the statistical analysis plan (SAP) for the NightstaRx-sponsored Protocol No. 273CH203 / NSR-REP-02: 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) (GEMINI Study).

AAV2-REP1 is denoted hereafter by the USAN timrepigene emparvovec (BIIB111).

This analysis plan is based on the final protocol dated 30 Oct 2019, incorporating the following versions/ amendments:

- Original protocol, dated 4 Jul 2017
- Amendment No. 1, version 2, dated 17 May 2018
- Amendment No. 2, version 3, dated 04 Feb 2019 (internal amendment only)
- Amendment No. 2.1, version 3.1, dated 19 Feb 2019
- Amendment No. 3, version 4, dated 30 Oct 2019

The SAP provides the description of the final analyses for the generation of the clinical study report.

2 Study Objectives and Endpoints

2.1 Objective

The objective of the study is to evaluate the safety of bilateral, sequential sub-retinal administration of a single dose of timrepigene emparvovec in adult male subjects with choroideremia (CHM).

2.2 Endpoints

2.2.1 Safety Endpoints

The safety of bilateral administration of timrepigene emparvovec will be evaluated with the following safety measures:

- Best Corrected Visual Acuity (BCVA) as measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart
- Ophthalmic examination assessments (including intraocular pressure [IOP], slit lamp examination, lens opacity grading and dilated ophthalmoscopy)
- Spectral domain optical coherence tomography (SD-OCT)
- Fundus autofluorescence
- Fundus photography
- Microperimetry
- Adverse Event (AE) reporting
- Vector shedding post-treatment
- Immunogenicity sampling post-treatment
- Vital signs

2.2.2 Secondary Efficacy Endpoints

- Change from Baseline in BCVA as measured by the ETDRS chart
- Change from Baseline in autofluorescence
- Change from Baseline in SD-OCT
- Change from Baseline in microperimetry

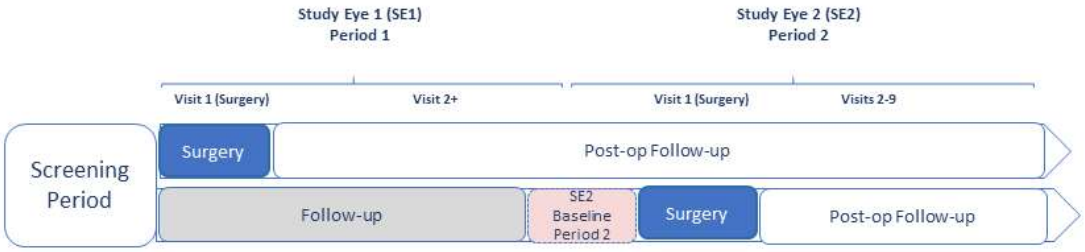
3 Study Design

3.1 Discussion of Study Design

This is a Phase 2, multi-centre, open-label, prospective, 2-period, bilateral interventional safety study of timrepigene emparvovec in adult male subjects with genetically confirmed CHM.

The study will consist of a Screening Period followed by 2 treatment periods (Period 1 and Period 2) with up to 9 visits per treatment period. A second baseline visit prior to surgery of Study Eye 2 (SE2) (Period 2, Visit 1) may be required. A study schematic is presented in Figure 1.

Figure 1 Overall Study Schematic



During the Screening Period, subjects will be assessed for eligibility of both eyes. The investigator will assign the order in which the eyes are treated (i.e., study eye 1 [SE1] period 1 and study eye 2 [SE2] period 2, respectively) with a number assigned to each eye. This will be done in collaboration with the subject; however, the worse eye will generally be selected for first treatment. The estimated target interval between the surgical procedures of SE1 and SE2 will be determined at the Screening Visit.

Each study eye will be followed for at least 12 months post-treatment, for up to 9 visits per treatment period: Visit 1 (Day 0, Injection Day Visit); Visit 2 (Day 1, post-operative follow up visit); Visit 3 (Day 3 + 2 Days); Visit 4 (Day 7 -1/+2 Days); Visit 5 (Day 14 ± 3 Days); Visit 6 (Month 1 ± 7 Days); Visit 7 (Month 3 ± 14 Days); Visit 8 (Month 6 ± 14 Days) and Visit 9 (Month 12 ± 14 Days).

The interval between SE1 and SE2 treatment is expected to vary among subjects from weeks to many months. While the interval will be decided on a case-by-case basis, an effort will be made to schedule varying treatment intervals in order to better characterise the immunological and safety profile of sequential treatment administration. Thus, approximately 20 subjects each will be treated with a short- (<6 month), medium- (6-12 months), or long- (>12 month) surgery window between treatment of the first and second eye. Because the timing of the second surgery visit (Period 2, Visit 1) will vary among subjects, the duration of study Period 1 will also be variable.

All baseline ophthalmic assessments must be conducted within 3 months prior to SE2 surgery (Period 2, Visit 1). If these assessments are not available within the required timeframe, a Baseline Visit must be added to collect current baseline data on SE2. If, at that time, BCVA in SE2 is <34 ETDRS letters, surgery may be performed when, in the opinion of the

investigator and after consultation with the sponsor: 1) the subject is found eligible by all other inclusion and exclusion criteria, and 2) the subject is considered an appropriate candidate who has potentially modifiable disease.

The post-operative outcome and visual function of SE1 will inform the scheduling of Period 2. Signs of post-operative inflammation or other post-operative sequelae, as judged by the investigator, should be resolved in SE1 for the subject to continue to Period 2. After comprehensive evaluation of all safety assessments and visual functional tests of SE1 and SE2, the Investigator will determine the eligibility of the subject and decide the appropriate time to schedule SE2, Visit 1.

Subjects who develop cataracts may undergo cataract surgery if deemed clinically necessary. If cataract surgery is performed, it should be carried out at least 4 weeks before Month 12 (Visit 9) for the respective eye. The cataract surgery timing must be discussed with the medical monitor prior to the procedure.

Subjects Previously Treated with Timrepigene Emparvovec

Subjects who have previously participated in a clinical trial of AAV2-REP1 for the treatment of CHM and have received AAV2-REP1 in one eye may be eligible for participation in this study. In these cases, only the subject's untreated eye will be assessed for eligibility. Following the Screening Visit and determination of eligibility, the subject will move directly into Period 2 for treatment of SE2.

3.2 Study Treatment

Eligible subjects will undergo vitrectomy and retinal detachment in each eye. At Period 1, Visit 1 (Day 0, the Injection Day Visit for SE1), subjects will receive in SE1 a sub-retinal injection of up to 0.1 mL of study drug containing 1×10^11 timrepigene emparvovec vg. At Period 2, Visit 1 (Day 0, the Injection Day Visit for SE2), subjects will receive in SE2 up to 0.1 mL of timrepigene emparvovec via sub-retinal injection.

3.3 Study Schedule

At Period 1, Visit 1 (Day 0, Injection Day Visit for SE1), subjects will undergo a vitrectomy with retinal detachment and receive a sub-retinal injection of timrepigene emparvovec in SE1. Visits 2-9 will then be conducted according to the Schedule of Study Procedures, unless Period 2 commences during the time of follow-up for SE1; in which case, the study visits will continue following the schedule for SE2. Ophthalmic assessments during Period 1, Visits 2-9 will be performed on both eyes.

At Period 2, Visit 1 (Day 0, Injection Day Visit for SE2), subjects will undergo a vitrectomy with retinal detachment and sub-retinal injection of timrepigene emparvovec in the contralateral, untreated eye (SE2). Post-treatment, subjects will no longer follow the Period 1 visit schedule, but will instead attend Period 2, Visits 2-9 according to the Schedule of Study Procedures. Ophthalmic assessments scheduled for Period 2, Visits 2-9 will be performed on both eyes.

Study data will thus be collected for both eyes in each subject. Subjects will be assessed for safety and efficacy throughout the study, as outlined in the Schedule of Study Procedures (Section 7.2).

A subject is considered to have completed the study if he completes Period 2, Visit 9 (Month 12). The end of the trial is the date the last subject completes Period 2, Visit 9 (Month 12) assessments (or early termination [ET] assessments in the event of premature discontinuation) or the date of last data collection if the last subject is lost to follow-up.

3.4 Randomisation

Not applicable for this study.

3.5 Blinding

Not applicable for this study.

3.6 Sample Size

Approximately 60 subjects are planned to be enrolled in the study. A total of 120 treated eyes is considered sufficient to characterise the immunological profile of bilateral timrepigene emparvovec administration, which is the key concern of gene therapy re-administration.

4 Statistical Methodology

4.1 Analysis Sets

The '**All Treated Subjects**' analysis set will consist of all subjects who complete the 'Day of Surgery' visit of Period 1 (or, of Period 2, for subjects who received timrepigene emparvovec treatment in SE1 in an antecedent study). All Treated Subjects analysis set will be the primary population for demographics, baseline characteristics, safety and efficacy analyses.

The '**Immunogenicity**' analysis set will include all subjects from the 'All Treated Subjects' analysis set with baseline sample and at least one post-surgery sample evaluable for immunogenicity. The Immunogenicity analysis set will be used for the immunogenicity analyses.

4.2 Conventions

Summary statistics will be presented for continuous variables, by way of number of subjects, mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3, respectively), 5th and 95th percentiles (P05 and P95, respectively), minimum and maximum. For categorical variables including binary variables, counts and percentages will be presented. Percentages will be calculated using the total number of eyes in the respective column or the total number of eyes with an assessment, the total number of treated subjects, depending on the nature of the analysis.

In addition, 95% 2-sided confidence intervals (CIs) will be presented, where specified. The 95% CI of the mean value of an assessment will be calculated using the t-test formula. The 95% CI of the mean of change from baseline of an assessment will be calculated using the t-test formula. In case of percentages, the CI will be computed using the Clopper-Pearson method. (See Section 4.21 for the corresponding SAS code).

No formal statistical comparison will be performed.

Summary statistics will be presented by period and overall for all endpoints. For selected endpoints (see details below), summary statistics will also be presented by Surgery Window (Short [<6 months], Medium [6-12 months] and Long [>12 months]) and overall. Where appropriate, summary statistics will be displayed by eye (SE1 and SE2), and by period.

4.3 Definitions

Study Eye 1 (SE1) is defined as the first treated eye (within GEMINI or in an antecedent clinical trial). **Study Eye 2 (SE2)** is defined as the second treated eye (irrespective of whether the first eye was treated in GEMINI or in an antecedent clinical trial). Subjects whose first eye is treated in an antecedent study will contribute to Period 2 only (except for the immunogenicity analyses), where Study Eye 1 is the eye treated in the antecedent study and Study Eye 2 is the eye treated in GEMINI.

Period 1 starts on the day of the surgery of the first treated eye and ends on the day prior to the day of the surgery of the second treated eye. **Period 2** starts on the day of the surgery of the second treated eye.

Baseline Value of **Period 1/2 is defined as** the last non-missing value prior to treatment of the respective period. Baseline of each period for each eye will be used to calculate the change from baseline for the data in the same period and same eye. For example, period 1 SE1 baseline will be used to calculate the change from baseline for all the data of SE1 in period 1, whereas period 2 SE1 baseline will be used to calculate the change from baseline for all the data of SE1 in period 2.

For immunogenicity, baseline will be defined separately in Section 4.17.11.

Analysis day for all the post-baseline visits will be calculated as the date of the post-baseline visits minus the corresponding injection date, depending on which baseline that was used.

For the 6 subjects whose first eye was treated in the antecedent study (Subjects [redacted]), only period 2 data are collected in GEMINI. Therefore, only period 2 data will be presented for these 6 patients.

Change from Baseline is defined as the difference of the value of an assessment at the considered visit from the baseline value of the corresponding period.

Duration is measured in days and is calculated as end date – onset date + 1.

Injection dates of SE1 and SE2 will be coded **Day 0** for the Period 1 and Period 2 respectively.

4.4 Data of Subjects with First Eye Treated in an Antecedent Study

For the 6 subjects who received timrepigene emparvovec treatment in their first eye in an antecedent study, the data from the antecedent study will not be included in the analyses presented in the Clinical Study Report (CSR).

4.5 Schedule of Analyses

At regular intervals during the study, the Data Monitoring Committee will review the progress and accrued study data and provide advice to the Sponsor on the efficacy and safety aspects of the study.

A final analysis will be conducted after all subjects complete the study.

4.6 Adjustment for Multiplicity

Not applicable for this study.

4.7 Subgroup Analysis

Demographic and baseline characteristics will be summarised by Surgery Site. The efficacy endpoints of BCVA will be summarised by the subgroups defined in Table 1.

Table 1 Subgroups Defined at Baseline

	Values
Age 1	≤50 years old >50 years old
Age 2	≤60 years old >60 years old
Age 3	<= median age >median age
Race	White Non-white (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander)
Region	America Europe
Surgery Site	Each of the surgery sites
Surgery Window	Short [<6 months], Medium [6-12 months] Long [>12 months] Overall

In addition, TEAE will also be summarized by Surgery Window (Short [<6 months], Medium [6-12 months] and Long [>12 months]) and all surgery windows combined.

4.8 Handling of Missing Values

The number, pattern and timing of missing data will be examined along with the reasons for withdrawal or for missing data.

The safety analyses will be performed using the 'observed case' method. In the efficacy analysis, observed case method will be applied as main analysis for categorical and continuous endpoints. The following supportive analysis will be performed for BCVA related endpoints: both categorical endpoints and continuous endpoints will be imputed using the 'Last Observation Carried Forward' (LOCF) method with the last available measurement prior to missing (see details in Section 4.16.1).

4.9 Statistical Analyses Handling of Data Impacted by COVID-19

Currently there is an outbreak of respiratory disease caused by a novel coronavirus (COVID-19). In terms of the statistical analysis, the impact of the COVID-19 pandemic on the GEMINI study will be evaluated by summarizing the number and percentage of subjects, by treatment and overall:

- Who died during the study due to COVID-19;
- Who withdrew from the study due to COVID-19;

The information for subjects who died during the study or withdrew from the study due to COVID-19 will be recorded in the eCRF.

4.10 Disposition of Subjects

The number of subjects who sign Informed Consent, who receive study treatment, who complete the study and the reasons for any premature discontinuation from the study will be presented. The number of subjects included in the All Treated Subjects analysis set and the Immunogenicity analysis set will also be presented. For each study visit, the number of subjects who attend the visit will be summarised.

4.11 Protocol Deviations

A summary table of protocol deviation will be provided which contains the number (%) of subjects with at least one protocol deviation. The table will also present the summary statistics for important protocol deviations (if defined). Similar table will be generated for COVID-19 related protocol deviation only.

4.12 Demographic and Baseline Characteristics

Demographic (sex, race, ethnicity, age [in years], age group [≤ 50 and > 50 years, ≤ 60 and > 60 years, ≤ median age and > median age]) and baseline characteristics (including weight) will be summarised in the All Treated Subjects analysis set. Baseline ocular characteristics will also be presented by eye (SE1 and SE2) and Period.

Demographic and baseline characteristics will also be summarised by Surgery Site in the All Treated Subjects analysis set.

Age is calculated as (Informed Consent date – date of birth + 1)/365.25 and presented to 1 decimal place. No rounding will be carried out prior to summarising age. Where the day and month of birth are not known, the date of birth will be assigned the value 30JUNYYYY.

4.13 Medical and Ocular History

Ocular History will be summarised by eye, by System Organ Class (SOC) and Preferred Term (PT), in the All Treated Subjects analysis set.

Where data are recorded as 'OU' (both eyes), the event will be attributed to both eyes (SE1 and SE2) for the purpose of the summary tables.

Medical History will be listed, with no summary table created.

Medical and ocular history will be coded according to the latest version (at the time of the data cut-off) of the Medical Dictionary for Regulatory Activities (MedDRA).

4.14 Prior and Concomitant Medication

Prior and concomitant (Ocular and Non-Ocular) medications will be presented in the All Treated Subjects analysis set by Anatomical Therapeutic Chemical (ATC) Level 4 and Preferred Term, and by Period for concomitant medications. Ocular medications will also be

presented by eye (SE1 and SE2). Where an ocular medication is recorded as 'OU', it will be counted once for each eye (SE1 and SE2).

Prior medications are those that start and stop before exposure to the treatment of SE1; concomitant medications are all medications taken from the day of first surgery, including those started before but ongoing at the time of the surgery.

The medication start and stop dates will be used to assign the medication to Period 1 or Period 2.

Imputation rules for partial dates are presented in Appendix 7.1.

Where a medication start date is partially or fully missing, and after imputation it is still unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant and will be attributed to SE1.

An eye with more than one occurrence of the same medication in a particular ATC class will be counted only once in the total of those with a report of medication in that particular ATC class.

Corticosteroid Treatment/Tapering will be listed. No summary table will be generated.

Medications will be coded according to WHO-Drug Dictionary (WHODD). The WHODD version will be the latest available at the time of the data cut-off.

4.15 Exposure

As the treatment consists of a single injection, exposure to study medication will not be evaluated.

4.16 Efficacy Analysis

Efficacy analysis will be performed in the All Treated Subjects analysis set.

4.16.1 Visual Acuity

Best-corrected visual acuity (BCVA) and change from baseline will be summarised by visit, by eye, by period as well as overall. The corresponding 95% CIs will be calculated (See Section 4.2).

Furthermore, the proportion of eyes with a ≥10 letters increase, a ≥15 letters increase, and an increase or a loss <5 letters (i.e. change from baseline >-5 letters) will be summarised by visit, by eye, by period as well as overall. The corresponding 95% CI will be presented (See Section 4.2).

The above main analyses will use the observed case method only. Imputation using LOCF method regardless of the reasons of missing data will be performed for supportive analyses (See Section 4.8).

In addition to the by-period, by-eye presentation mentioned above, as supportive analyses, for both continuous and categorical endpoints, the period 2 Study Eye 1 data will be presented by

remapping them to visits after their last visit in period 1 and calculating change from baseline using baseline at period 1 for the same eye (Study Eye 1). This way a full picture of Study Eye 1 treatment journey during the entire study will be presented.

For all assessments of periods 1 and 2 of Study Eye 1, the data records will be assigned to calculated visit window (using study day) as described in Table 2 below. The window of the visits following baseline (including unscheduled visits) will be constructed in such a way that the upper limit of the interval falls half way between the two visits.

If a patient has more than one assessment included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target date, the value with the later date will be used.

Table 2 Visit Assignment Windows

Day / Month	Target Day	Day Range included in the visit
Baseline	0	The last assessment on or before day 0
Day 1	1	Day 1
Day 3	3	Day 2 to 5
Day 7	7	Day 6 to 10
Day 14	14	Day 11 to 22
Month 1	30	Day 23 to 61
Month 3	91	Day 62 to 136
Month 6	182	Day 137 to 272
Month 9	273	Day 228 to 318
Month 12	365	Day 319 to 410
Month 15	456	Day 411 to 501
Month 18	548	Day 502 to 593
Month 21	639	Day 594 to 684
Month 24	731	Day 685 onwards

Both continuous and categorical endpoints for BCVA will be summarised by subgroups mentioned in Section 4.7.

4.16.2 Fundus Autofluorescence

Observed value, change from baseline, and percent change from baseline for Total Area of Preserved AF, square root of the Total Area of Preserved AF and Distance from Foveal Center (FC) to nearest Border of Preserved AF will be summarised by visit, by eye, and by period.

The number and percentage of subjects with Subfoveal or non-Subfoveal Lesion in Relation to FC will be summarised by visit, by eye, and by period.

Shift from baseline in Lesion will be summarised by calculating the number of subjects falling in each of the following categories:

- Not subfoveal at Baseline to Not subfoveal
- Not subfoveal at Baseline to Subfoveal
- Subfoveal at Baseline to Not subfoveal
- Subfoveal at Baseline to Subfoveal

Those summaries will be presented by visit, by eye and by period.

For Subfoveal or non-Subfoveal Lesion in Relation to FC, 'Subfoveal' will be assigned as the 'worst case' value.

Image quality will be listed only. This includes image completeness, focus/clarity, field definition, exposure, contrast and 'Is the total area of preserved AF fully captured within frame'.

Note: The variable 'Distance from FC to nearest Border of Preserved AF' takes a positive value when 'Location of Lesion in Relation to FC' is Not Subfoveal and a negative value when 'Location of Lesion in Relation to FC' is Subfoveal.

4.16.3 Spectral-Domain Optical Coherence Tomography

Observed value, change from baseline, and percent change from baseline for Foveal Subfield Thickness, Total Macular Volume, Central Horizontal Ellipsoid Width, Central Ellipsoid Area, the square root of the Central Ellipsoid Area and Choroidal Thickness at Foveal Center will be summarised by visit, by eye, and by period.

Presence of Vitreomacular Traction (VMT), Epiretinal Membrane (ERM), Macular Hole (MH), Intraretinal Hyper-Reflective Spots, Cystoid Macular Edema, Subretinal Fluid (SRF), Subretinal Hyper-Reflective Material and Pigment Epithelial Detachment will be summarised by visit, by eye, and by period. Shift from baseline will be evaluated for each of these assessments.

The categories for the shift from baseline for VMT, ERM, MH and Intraretinal Hyper-Reflective Spots assessments are defined as follow:

- Absent at Baseline to Absent
- Absent at Baseline to Present
- Present at Baseline to Absent

- Present at Baseline to Present

The categories for the shift from baseline for Cystoid Macular Edema, SRF, Subretinal Hyper-Reflective Material and Pigment Epithelial Detachment assessments are defined as follows:

- None at Baseline to None
- None at Baseline to Yes, foveal/Yes, non-foveal
- Yes, foveal/Yes, non-foveal at Baseline to None
- Yes, foveal/Yes, non-foveal at Baseline to Yes, foveal/Yes, non-foveal

For VMT, ERM, MH and Intraretinal Hyper-Reflective Spots, 'Presence' will be assigned as the 'worst case' value. For Cystoid Macular Edema, SRF, Subretinal Hyper-Reflective Material and Pigment Epithelial Detachment, 'Yes, foveal/Yes, non-foveal' will be assigned as the 'worst case' value.

Image quality will be listed only. This includes the Image Completeness, Centration, Tilt, Motion Artifacts and Signal Strength.

4.16.4 Macular Integrity Assessment Microperimetry

Mean Sensitivity, Bivariate Contour Ellipse Area 63%, Bivariate Contour Ellipse Area 95% and Fixation Losses will also be summarised by visit, by eye, by period as well as overall. The corresponding 95% CIs will be calculated (See Section 4.2).

The number and percentage of subjects within each category of Fixation Stability will be summarised by visit, by eye, by period and by surgery window as well as all surgery windows combined. Shift from baseline will also be evaluated.

The categories for the shift from baseline for 'Fixation Stability' assessment are defined as follows:

- Stable at Baseline to Stable
- Stable at Baseline to Relatively Unstable/Unstable
- Relatively Unstable/Unstable at Baseline to Stable
- Relatively Unstable/Unstable at Baseline to Relatively Unstable/Unstable

Where microperimetry data are collected using the automated text files, the following algorithm will be used to define the value of Fixation Stability.

- If P1≥75%, then fixation stability is considered as stable.
- If P1<75% and P2≥75%, then fixation stability is considered as relatively unstable.
- If P1<75% and P2<75%, then fixation stability is considered as unstable

Image quality will be listed only. This includes image completeness, focus/clarity and field definition.

4.17 Safety Analysis

Safety analysis will be performed on the All Treated Subjects analysis set using observed cases only.

4.17.1 Visual Acuity

The proportion of eyes with a ≥5 letters, a ≥10 letters and a ≥15 letters decrease from baseline (i.e. change from baseline ≤-5, -10 and -15 letters, respectively) will be summarised by visit, by eye, by period as well as overall in the same categorical summary tables mentioned in Section 4.16.1. The corresponding 95% CI will be presented (See Section 4.2).

4.17.2 Intraocular Pressure

Intraocular pressure and change from baseline will be summarised by visit, by eye, by period as well as overall.

4.17.3 Slit Lamp Examination

The number and percentage of subjects within each category of Slit Lamp Examinations outcomes will be summarised by visit, by eye, by period as well as overall. Shift from baseline will also be evaluated.

The categories for the shift from baseline for 'Cornea', 'Conjunctiva', 'Iris', 'Lens' and 'Anterior Segment' assessments are defined as follows:

- Normal/Clinically insignificant abnormality at Baseline to Normal/Clinically insignificant abnormality
- Normal/Clinically insignificant abnormality at Baseline to Clinically significant abnormality
- Clinically significant abnormality at Baseline to Normal/Clinically insignificant abnormality
- Clinically significant abnormality at Baseline to Clinically significant abnormality

The categories for the shift from baseline for 'Anterior chamber, hypopyon', 'Grading of anterior chamber cells', 'Grading of anterior chamber flare' and 'Vitreous inflammation quantification' assessments are defined as follows:

- Absent at Baseline to absent
- Absent at Baseline to present
- Present at Baseline to absent
- Present at Baseline to present

For 'Grading of anterior chamber cells' assessment, absent is defined as '0 Cells' and present is defined as any other category (except missing).

For 'Grading of anterior chamber flare' assessment, absent is defined as 'Complete absence' and present is defined as any other category (except missing).

For 'Vitreous inflammation quantification' assessment, absent is defined as '0' and present is defined as any other category (except missing).

4.17.4 Lens Opacity Grades

The number and percentage of subjects within each category of Nuclear Opalescence Grade, Nuclear Colour Grade, Cortical Cataract Grade and Posterior Cataract Grade will be summarised by visit, by eye, by period as well as overall. Shift from baseline will also be evaluated.

The categories for Lens Opacity Grades are defined as Category 1, 2, 3 and 4. 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. Category 4 includes values 4, 4.0, 3.x an any values above 4.

The categories for the shift from baseline are defined as follows:

- No change in category
- Decrease in category
- Category 1 at Baseline to Category 2, 3 or 4
- Category 2 at Baseline to Category 3 or 4
- Category 3 at Baseline to Category 4

4.17.5 Dilated Ophthalmoscopy

The number and percentage of subjects within each category of each Dilated Ophthalmoscopy outcomes will be summarised by visit, by eye, by period as well as overall. Shift from baseline will also be evaluated.

The categories for the shift from baseline for 'Vitreous', 'Macula', 'Peripheral retina', 'Choroid' and 'Optic nerve' assessments are defined as follows:

- Normal/Clinically insignificant abnormality at Baseline to Normal/Clinically insignificant abnormality
- Normal/Clinically insignificant abnormality at Baseline to Clinically significant abnormality
- Clinically significant abnormality at Baseline to Normal/Clinically insignificant abnormality
- Clinically significant abnormality at Baseline to Clinically significant abnormality

The categories for the shift from baseline for 'Retinal tear(s)' and 'Retinal detachment' assessments are defined as follows:

- Absent at Baseline to absent

- Absent at Baseline to present
- Present at Baseline to absent
- Present at Baseline to present

4.17.6 SD-OCT

See Section 4.16.3.

4.17.7 Fundus Autofluorescence

See Section 4.16.2.

4.17.8 Fundus Photography

Presence and severity of Retinal Pigment Epithelium (RPE) Hyperplasia, Retinal Arteriolar Narrowing, Retinal Vessel Sheathing, Optic Atrophy/Pallor and Optic Disc Swelling will be summarised by visit, by eye, and by period. Shift from baseline will also be evaluated.

The categories for the shift from baseline are defined as follows:

- Absent at Baseline to absent
- Absent at Baseline to present
- Present at Baseline to absent
- Present at Baseline to present

where Absent corresponds to None and Present to Mild, Moderate or Severe.

Image quality will be listed only. This includes image completeness, focus/clarity, field definition, stereopsis, exposure and contrast.

4.17.9 Microperimetry

See Section 4.16.4.

4.17.10 Adverse Events

Treatment Emergent Adverse Events (TEAEs) are defined as AEs starting on or after the day of the first surgery. AEs reported in subjects who received timrepigene emparvovec treatment in their first eye in an antecedent study will be considered as TEAEs. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is. Summary tables will include TEAEs only. TEAEs will be summarised by eye (for ocular events), by period, and overall. Each by-period summary table will be repeated by surgery window instead.

The number and percentage of subjects reporting any event, any non-ocular event, any ocular event, any ocular event in SE1 and any ocular event in SE2 will be summarised. Percentage will be calculated based on the number of subjects in the corresponding period or surgery window or overall. The 95% CI will be calculated using the Clopper-Pearson method.

Overall summary table of TEAE by period (or by surgery window) will be provided for the following categories:

- Number and percentage of subjects with a TEAE
- Number and percentage of subjects with a serious TEAE
- Number and percentage of subjects with a Treatment-related (study drug or study procedure) TEAE
- Number and percentage of subjects with a Treatment-related (study drug or study procedure) serious TEAE
- Number and percentage of subjects with a TEAE leading to death
- Number and percentage of subjects who discontinued due to a TEAE
- Number and percentage of subjects with a TEAE by severity
- Number and percentage of subjects with a TEAE by outcome
- Number and percentage of subjects with a TEAE by action taken

Adverse events will be summarized by period (or by surgery window), and overall. The following summaries of TEAEs will be provided:

- TEAEs by SOC and PT
- TEAEs by PT with percentage ≥ 5%
- Treatment-related (study drug or study procedure) TEAEs by SOC and PT
- Study procedure-related TEAEs by SOC and PT
- Study drug-related TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity (missing severity, if any, will be counted as severe).
- Serious TEAEs by SOC and PT
- Treatment-related (study drug or study procedure) serious TEAEs by SOC and PT
- Study procedure-related serious TEAEs by SOC and PT
- Study drug-related serious TEAEs by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs reported by subjects who discontinued due to SAE by SOC and PT

Both counts of subjects and events will be reported. A subject with more than one occurrence of the same AE in a particular SOC will be counted only once in the total of those experiencing AEs in that particular SOC.

If a subject experiences the same AE at more than one severity, the most severe rating will be given precedence.

If a subject experiences the same AE at more than one relationship to study drug/procedure, causal relationship will be given precedence over no causal relationship. However, where a causal relationship is identified by the Investigator, the subject will be counted once within each sub-category (Study Drug, Study Procedure, Study Drug and Study Procedure, unknown).

In the summary tables, related events are defined as events that are assessed by the investigator to be related to study drug/procedure/both or with an unknown relationship.

AEs will be assigned to Period 1 or Period 2 based on the AE Start Date. An AE with a start date on or after the day of surgery of Study Eye 2 will be attributed to Period 2; otherwise, the AE will be attributed to Period 1.

An ocular event is an event where the site of the event is reported as OU, OD or OS. Where an event is recorded as 'OU', it will be counted once for each eye (SE1 and SE2).

Separate additional summaries will be provided for adverse events classified as Ocular Inflammation and Visual Acuity Reduced. The lists of PTs assigned to Ocular Inflammation and Visual Acuity Reduced are provided in a separate document (BIIB111 Signal Detection Plan). The following summaries will be provided by eye, by period (or by surgery window), and overall:

- Ocular Inflammation-related TEAEs by SOC and PT
- Ocular Inflammation-related TEAEs by SOC and PT, and by time to onset (≤30 days; >30 days)
- Visual Acuity Reduced-related TEAEs by SOC and PT
- Visual Acuity Reduced-related TEAEs by SOC and PT, and by time to onset (≤30 days; >30 days)

Imputation rules for partial dates are presented in Appendix 7.1.

The following listings will be provided:

- All AEs
- AEs leading to death

AEs will be coded according the MedDRA version 23.0 or higher.

4.17.11 Immunogenicity

Immunogenicity analyses will be performed on the Immunogenicity Analysis Set. Three immunogenicity data sets will be analyzed for the study: Anti-Drug Antibodies (ADA) to the transgenic product (REP1), neutralizing timrepigene emparvovec antibodies (Nabs) and ELISpot.

In the ELISpot assay, a subject will be tested using 4 different analytes peptide pools (REP1 Pool 1, REP1 Pool 2, REP2 Pool 3, AAV2) at each visit. All 4 pools together are used to evaluate the immune response to the whole therapeutic product, BIIB111, in which, the 3 REP1 pools are used to evaluate the immune response to the therapeutic gene product, and the AAV2 pool is used to evaluate the immune response to the AAV vector. A subject will be determined to have a positive result to the overall treatment with BIIB111 if any of the 4 analytes is positive. A subject will be determined to have a positive result with respect to the REP1 if any of the 3 REP1 result is positive. A subject will be determined to have a positive result with respect to the AAV2 if the AVV2 analyte is positive.

Samples with a numeric titer are considered as positive for ADA or Nabs respectively. For ELISpot, only samples which have spot counts (presented as SFU=spots per 1 mio cells) 3-fold of control (which is SFU of untreated cells) will present as positive.

All the immunogenicity analyses specified in this section will be performed by assays (ADA, Nabs, ELISpot).

4.17.11.1 Baseline Definition

As the second eye treatment in Period 2 in GEMINI may potentially increase the risk of a subject developing an immune response against the therapeutic product, BIIB111, we define two different types of baselines to evaluate the treatment emergent immune response, anchored to the time when the first eye was treated, and when the second eye was treated, respectively. The definition is as below.

Period 1 baseline is defined as the last available value prior to surgery of the first eye. For subjects without any assessments prior to surgery of the first eye, Day 1 sample will be used as baseline. If neither assessment prior to surgery of the first eye nor Day 1 sample are available, the period 1 baseline is set missing.

Period 2 baseline is defined as the last available value within 10 weeks prior to the surgery of the second eye. For subjects without any assessments within 10 weeks prior to surgery of the second eye, Day 1 sample post-second eye surgery will be used as baseline for period 2. If neither assessment prior to surgery of the second eye nor Day 1 sample are available, the period 2 baseline is set missing.

Note that the immunogenicity data is collected as one record per subject per visit.

4.17.11.2 Assay Positivity by Visit

The number and percentage of subjects with positive results at each visit will be presented by baseline status (such as screen positive, negative etc) and by treatment group. The positivity analysis for ELISpot will be summarized for the overall treatment of BIIB111 as well as with respect to either REP1 or AAV2.

4.17.11.3 Assay Treatment-emergent Analysis by Visit

The number and percentage of subjects with a positive result will be further tabulated by treatment-emergent status (see definition below, treatment-emergent and non-treat-emergent positive) by, visit, period, surgery windows, and surgery windows combined.

A treatment-emergent positive result is defined as follows for ADA and Nabs:

- A post-baseline result that is positive when the baseline result is negative.
- A post-baseline result that has a titer greater than or equal to 4 times the baseline titer when the baseline result is positive, while titer values are available at both baseline and post-baseline visits.

For ELISpot, the treatment-emergent positive for each analyte is defined as a post-baseline result that is positive when the baseline result is negative. If any of the 3 REP1 analytes is treatment-emergent positive, it is a treatment-emergent positive for REP1. The treatment-emergent positive for AAV2 is defined as a post-baseline result that is positive when the

baseline result is negative for the AAV2 analyte. If either REP1 or AAV2 is treatment-emergent positive, it is a treatment-emergent positive for the overall treatment of BIIB111. The treatment-emergent analysis for ELISpot will be summarized for the overall treatment of BIIB111 as well as with respect to either REP1 or AAV2.

If either the valid baseline samples (see definition above, prior to surgery or Day 1) or valid post-baseline samples at a particular visit are not available, the subject will be assigned as missing for treatment-emergent status at that particular visit and excluded from the treatment-emergent assessment. The remaining available valid baseline samples and post-baseline assessments will be tabulated and contribute to the positive/negative overtime summary mentioned in 14.15.11.2. Invalid sample results include but are not limited to "Quantity Not Sufficient", "No Results", etc and will be deemed missing.

For analyses on treatment-emergent immunogenicity, period 1 baseline will be used to derive the change from baseline for data of period 1 visits (before 2nd eye injection) and period 2 baseline will be used to derive the change from baseline for data of period 2 visits (post 2nd eye injection).

4.17.11.4 Relationship Between Immunogenicity Assay and Safety

The relationship between the immunogenicity assays (ADA, Nab and ELISpot) and selected adverse events will be assessed. These adverse events include ocular inflammation-related adverse events, visual acuity reduced-related adverse events and hypersensitivity-related adverse events. The number and percentage of post-treatment (treatment-emergent) ocular inflammation-related adverse events, visual acuity reduced-related adverse events and hypersensitivity-related adverse events (based on the adverse event data), as well as the number and percentage of eyes with a decrease from baseline of ≥15 letters in BCVA at Month 12 (based on the visual acuity assessment data) will be summarized by (1) subjects with negative assay at period 1 baseline; and (2) subjects with positive assay at period 1 baseline; and (3) subjects with at least one treatment-emergent positive assay at any visit during the study; and (4) subjects with no treatment-emergent positive assay during the study. In (3) and (4), to determine the treatment-emergent positivity, the period 1 baseline will be used to calculate the change from baseline for data in period 1 and period 2 baseline will be used to calculate the change from baseline for data in period 2.

The analyses will be conducted by eye, by period and surgery window. It will be repeated by AE severity (mild, moderate and severe) and by AE time to onset (≤30 days and >30 days post-surgery). If an AE has more than one occurrence with an onset ≤30 days and another >30 days, the AE will be reported in both ≤30 days and >30 days' time to onset categories.

4.17.11.5 Data Listing

Individual subject data will be listed with their positive/negative status, titer information (spot forming units (SFU) for ELISpot assay) and AEs of interests (as mentioned above) where available. The impact of assay status (positive/negative, treatment-emergent positive yes/no) on clinical efficacy may be further evaluated if needed.

4.17.12 Vector Shedding

Samples of vector shedding will be summarized by categorical results and will be tabulated by visit, by period and eyes. Categorical results include but not limit to Positive, Negative and Below the Level of Quantification. The data of vector shedding will be listed.

4.17.13 Vital Signs

Blood pressure and pulse rate and change from baseline will be summarised by visit and by period.

4.18 Protocol Violations or Deviations

Deviations from the protocol will be documented on an ongoing basis by the study monitors/project manager throughout the study period.

4.19 Deviations from the Statistical Analysis Plan

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

4.20 Changes in Planned Analyses from the Protocol

There are some changes to the planned analyses described in the protocol.

1. The protocol refers to the assessment of Fixation Location. Because of a change in the way microperimetry data are collected, fixation location is not available in the database. Therefore, Fixation Location was removed from the SAP.
2. The protocol mentions that specific analyses of the sensitivity points (microperimetry) will be performed. These analyses are not included in the SAP as they are considered as exploratory across the BIIB111 program and will be performed as post-hoc analyses, if needed to be consistent with other studies in the same program.
3. For consistency of other studies in the program, time to resolution of AEs will not be summarized.
3. The protocol specifies that LOCF will be used as imputation method for efficacy analyses. The main analyses of categorical and continuous efficacy endpoints will use the observed case method, as the main purpose of the study is the evaluation of BCVA from a safety perspective. Additional supportive analyses of BCVA-related endpoints, including LOCF imputation, will be applied and are described in detail in Section 4.16.1.

4.21 Algorithms/SAS Codes

- **Descriptive statistics for continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
   VAR var1 var2 var3 …varn;
   BY byvar; (optional)
   OUTPUT OUT=outname
   N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std
   P5=p5 P95=p95 Q1=q1 Q3=q3;
RUN;
```

- **95% CIs for continuous variables – ttest formula:**

```
DATA outdata;
   SET outname;
   LCL=mean-(TINV(0.975,n-1)*(std/SQRT(n)));
   UCL=mean+(TINV(0.975,n-1)*(std/SQRT(n)));
RUN;
```

- **Frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
   BY byvar; (optional)
   TABLES var1*var2;
   OUTPUT OUT=outname;
RUN;
```

- **Clopper-Pearson 95% CIs within group for binomial proportions:**

```
DATA outdata;
   SET outname;
   p=round ((x/n),0.0001);
   if p=0 then LCL=0;
   if p=1 then UCL=1;
   if p ne 0 then LCL=round((1-betainv(.975,(n-x+1),x)),.0001);
   if p ne 1 then UCL=round((1-betainv(.025,(n-x),x+1)),.0001);
RUN;
```

5 Tables and Listings

5.1 Format

All outputs will be produced using SAS version 9.4 or a later version.

A header will include the following text: `NightstaRx, Ltd NSR-REP-02 <FINAL ANALYSIS>`

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

Outputs will be produced as rtf files. The output file name will include the table number and name.

5.2 Conventions for output display

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the SD will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

Any date information in the listing will use the date9. format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. **Listings should be sorted by subject number, eye (starting with Study Eye or Study Eye 1) and visit.** Listings should have the source data received from data management referenced in a footnote.

6 References

MAIA, Macular Integrity Assessment, Microperimetry Handbook, First Edition, Centervue.

7 Appendices

7.1 Appendix 1 – Imputation of Partial Dates

These imputation rules are limited to AE and CM partial dates only.

Partial start dates (of intervention or event)

- Case 1, day is missing (only month and year are present):
  - If year and month are same as treatment period start date then assign the day of treatment period start date to the partial date.
  - However, if end date of event or intervention is clearly before treatment period start date, assign day '01' to partial start date.
  - Otherwise, assign day of '01' to partial start date.
- Case 2, only year is present:
  - If year is same as treatment period start date then assign the month and day of the treatment period start date to the partial date.
  - However, if end date of event or intervention is clearly before treatment period start date, assign 'Jan. 01' to partial start date.
  - Otherwise, assign the month and day of 'Jan. 01' to partial start date.
- Case 3, completely missing date, no imputation is performed.

Partial end dates (of intervention or event)

- Case 1, day is missing (only month and year are present):
  - If year and month are same as study end date then assign the day of the study end date to the partial date.
  - Otherwise, assign day of last day of the month (28, 29, 30 or 31) to the partial end date.
- Case 2, only year is present:
  - If year is same as study end date then assign the month and day of the study end date to the partial date.
  - Otherwise, assign 'Dec. 31' to the partial end date.
- Case 3, completely missing date, no imputation is performed.

Note: If any partial dates have missing month, with day present, then day is ignored and also considered missing. Similarly, if year is missing, with day or month present, we handle as if the entire date is missing.

Note: If the study is ongoing and study end date is not available then the cut-off date will be used in the place of study end date. If both a cut-off date and study end date are present for a patient then the minimum of the two dates will be used as the study (or reference) end date.

7.2 Schedule of Study Procedures

Table 3 presents a schedule of study procedures.

Table 3 Schedule of Study Procedures

Visit	Period 1 Screening[a]	Period 2 Baseline[b] (<12 Weeks from Visit 1, Period 2)	Study Period 1 / Period 2									ET Visit[d]	Unscheduled Visit[e]
			V1	V2	V3	V4	V5	V6	V7	V8	V9		
Study Day/Month Visit Window			**Day 0 Injection Day[c] (≤10 weeks Screening)**	**Day 1 Post op**	**Day 3 Post op**	**Day 7 ± 1d**	**Day 14 ± 3d**	**M 1 ± 7d**	**M 3 ± 14d**	**M6 ± 14d**	**M 12 ± 14d**		
Assessment/Procedures (All subjects/eyes)													
Informed Consent	X												
Demography, medical and ocular history	X												
Vital signs (pulse, blood pressure)	X	X		X	X						X	X	
Weight[f]	X	X											
Vector shedding sampling[g]	X	X		X	X	X	X	X	X			X[h]	
Immunogenicity sampling[i]	X	X		X		X	X	X	X	X	X	X	
BCVA	X	X		X	X	X	X	X	X	X	X	X	X
Microperimetry	X	X						X	X	X	X	X	
Full ophthalmic exam[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X		X		X	X	X	X	X	X	X	X
Autofluorescence	X	X				X	X	X	X	X	X	X	
7-field colour fundus photos[k]	X	X									X	X	
Study drug / sub-retinal injection / vitrectomy / retinal detachment			X										
AE/SAE monitoring[l]	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Period 1 Screening[a]	Period 2 Baseline[b] (<12 Weeks from Visit 1, Period 2)	Study Period 1 / Period 2									ET Visit[d]	Unscheduled Visit[e]
			V1	V2	V3	V4	V5	V6	V7	V8	V9		
Study Day/Month Visit Window			Day 0 Injection Day[c] (≤10 weeks Screening)	Day 1 Post op	Day 3 Post op	Day 7 ± 1d	Day 14 ± 3d	M 1 ± 7d	M 3 ± 14d	M6 ± 14d	M 12 ± 14d		
Assessment/Procedures (All subjects/eyes)													
Concomitant medication, procedures, and treatment review[m]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; BCVA=best corrected visual acuity; ET=early termination; IOP=intraocular pressure; LOCS=lens opacities classification system; SAE=serious adverse event; SD-OCT=spectral domain optical coherence tomography; SE1=Study Eye 1; SE2=Study Eye 2

[a] Screening Visit/Period must be performed ≤10 weeks of Period 1, Visit 1. Selection of SE1 and SE2 will be determined by the investigator in collaboration with the subject.

[b] Baseline assessments must occur before the SE2 is dosed. These can occur at a regularly scheduled visit if that visit is within 12 weeks prior to surgery in SE2. If it has been more than 12 weeks since a visit, the subject must return for assessments at this Baseline Period 2 visit. Similarly, for subjects who have previously been treated unilaterally with timrepigene emparvovec in an antecedent study, these baseline assessments must be performed within 12 weeks prior to surgery on Visit 1, Period 2. A separate visit is only required if the assessments have not been performed within 12 weeks prior of surgery in SE2.

[c] Subjects will undergo vitrectomy and timrepigene emparvovec administration to SE1 in Period 1; SE2 in Period 2.

[d] ET visit is to be performed if a subject discontinues at any time.

[e] If clinically indicated, subjects may need to return to the site for an unscheduled visit. At a minimum, the following assessments will be performed: BCVA, full ophthalmic examination, SD-OCT, AF, concomitant medication, procedures and treatment review and AE/SAE monitoring.

[f] Weight is collected for dose calculation of the corticosteroid regimen.

[g] Blood, tears (both eyes), urine and saliva samples.

[h] If ET visit occurs within 3 months post-treatment.

[i] Immunoassays are planned to assess cell-based and antibody-based immune responses against timrepigene emparvovec. Enzyme-linked immunospot (ELISPOT) assays will be used for the assessment of T-cell-mediated immune responses to transgene product (REP1) and the capsid. Antibody responses against the capsid and transgene product will be measured using a cell-based neutralization assay and an enzyme-linked immunosorbent assay (ELISA), respectively. All immunogenicity samples will be sent to a central laboratory for analysis.

[j] The ophthalmic examination will include IOP, slit lamp examination, lens opacity grading, and dilated ophthalmoscopy. The same slit lamp machine and lighting conditions should be used across the study for each subject.

[k] Stereo photos for fields 1, 2, 3.

[l] AEs/SAEs will be collected from the time the subject provides written informed consent (Screening Visit) through Period 2, Visit 9 (or ET Visit, if applicable).

[m] Subjects will be given a course of oral corticosteroid before each surgical visit, and instructed to start taking the drug 2 days prior to SE1/SE2 treatment, unless the SE2 surgical treatment coincides with the SE1 steroid treatment period, when an extended course of steroid can cover both surgical treatments. For SE1, the Full Corticosteroid Regimen should be initiated as described. For SE2, and surgeries that occur on day 21 or later, the Full Corticosteroid Regimen should be initiated as described, beginning 2 days before the scheduled SE2 surgery. If SE2 is to be performed prior to Study Day 21, then the Full Corticosteroid Regimen should be initiated 2 days prior to the scheduled surgery for SE2, and this will supersede the steroid taper in progress for SE1. The full 21 days of treatment will then be completed for SE2.