COVER PAGE

Official Title:	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)
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Statistical Analysis Plan

STAR Study

PROTOCOL: **273CH301 / NSR-REP-01 (Timrepigene emparvovec)**

A Randomized, 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)

INDICATION: Choroideremia

STUDY PHASE: 3

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SPONSOR: Biogen
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SPONSOR APPROVAL SIGNATURES

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Date 11FEB2021

The persons listed below are authorized to sign the Statistical Analysis Plan for this study, 273CH301 / NSR-REP1-01, on behalf of Biogen / NightstaRx Ltd.

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ABBREVIATIONS

AAV	adeno-associated viral vector
AAV2	AAV serotype 2
AAV2-REP1	AAV2 virus particle encapsulating 1.962kB cDNA of the wild-type human REP1 gene
ADA	anti-drug antibodies
AE	adverse event
AF	autofluorescence
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BCVA	best corrected visual acuity
CHM	choroideremia
CI	confidence interval
COVID-19	coronavirus disease 2019
CRC	Central Reading Center
CRF	case report form
CSS	contrast sensitivity score
DBL	database lock
DMC	Data Monitoring Committee
ERM	epiretinal membrane
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	fundus autofluorescence
FC	foveal center
FCS	fully conditional specification
FM	Farnsworth-Munsell
IOP	intraocular pressure
IReST	international reading speed texts
ITT	Intent-to-Treat
LLD	low luminance deficit
[redacted]	[redacted]
LOCF	last observation carried forward
MAR	Missing at Random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MH	macular hole
MI	multiple imputation
MP	microperimetry
MMRM	mixed model for repeat measurements
MNAR	Missing Not at Random
OD	oculus dextrus (right eye)
OS	oculus sinister (left eye)
OU	oculus uterque (both eyes)

P05	5th percentile
P95	95th percentile
PBMC	peripheral blood mononuclear cells
PP	per protocol
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
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SFU	spot forming units
SOC	system organ class
SRF	subretinal fluid
TEAE	treatment-emergent adverse event
TOF	targeted ocular findings
VFQ	visual function questionnaire
vg	viral genomes
VMT	vitreomacular traction
WHO	World Health Organisation
WHODD	Who-Drug Dictionary

1 INTRODUCTION

This document presents the statistical analysis plan (SAP) for Biogen / NightstaRx Ltd, Protocol No. 273CH301 / NSR-REP-01: A Randomized, 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 Study).

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

The purpose of this SAP is to ensure that the efficacy and safety analyses prespecified by statistical methodologies provide appropriate definitions for summary tables, figures, and data listings.

2 STUDY OBJECTIVES

The objective of the study is to evaluate the efficacy and safety of a single sub-retinal injection of timrepigene emparvovec in subjects with choroideremia (CHM).

3 OVERVIEW OF STUDY DESIGN

3.1 Discussion of Study Design

This is an outcomes-assessor masked, prospective, randomized, parallel- controlled group, multi-center, global, interventional study. The study consists of 8 visits with a 12-month evaluation period (Figure 1). During the Screening/Baseline Period, each subject will be assessed for eligibility. If a subject has only 1 eligible eye, that eye will be designated as the "study eye" and the subject's other (non-eligible) eye will be designated as the "fellow eye." If a subject has 2 eligible eyes, the selection of the "study eye" will be made on clinical grounds and will generally be the worse eye affected.

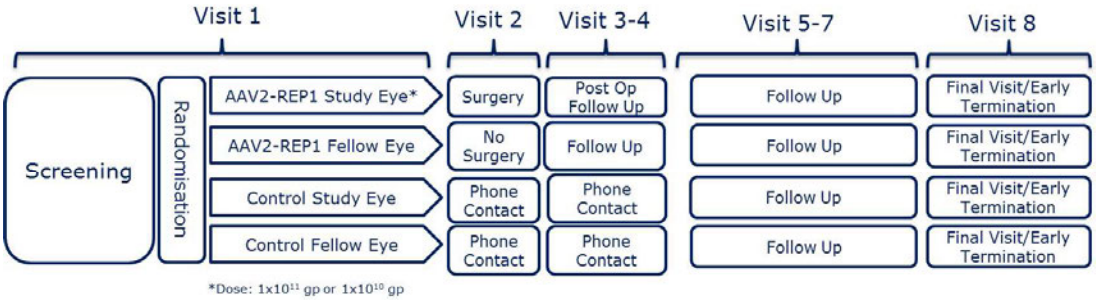
For eligible subjects, a study eye will be assigned, and the subjects will be randomized in a 2:1:2 ratio to receive either timrepigene emparvovec high dose (1.0×10^{11} viral genomes [vg]), timrepigene emparvovec low dose (1.0×10^{10} vg) or to enter the untreated Control group. Once a subject has been randomized, a change in "study eye" designation is not permitted.

At the time of randomization, a projected surgical date should be defined for each subject. For each subject randomized to the control group, this projected surgical date (+/- 1 day) should remain the Day 0 (Visit 2) date. For each subject randomized to a treated group, Day 0 (Visit 2) will be the actual date of surgery. The Screening / Baseline period must occur within 8 weeks prior to dosing (Week 2, Day 0).

Study data will be collected for both eyes of each subject.

Since timrepigene emparvovec treatment requires an invasive surgical procedure under general anesthesia, the sponsor, investigator and the subject will be unmasked to the study procedure (i.e. vitrectomy and sub-retinal injection), however within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^{11} vg or 1.0×10^{10} vg). To further minimize the potential bias of the treated and untreated eye evaluations, all subjective ophthalmic assessments from the Screening/Baseline period (Visit 1) and from Month 1 (Visit 5) onwards, will be conducted by a masked assessor.

Figure 1 Overall Study Schematic



3.2 Study Treatment

The AAV2 vector contains recombinant human cDNA encoding REP1 (timrepigene emparvovec). The vector genome (AAV2-CBA-hREP1-WPRE-BGH) consists of a strong constitutive expression cassette, a hybrid chicken beta actin promoter, the human cDNA encoding Rab escort protein-1 (REP1), a modified woodchuck hepatitis post-transcriptional regulatory element sequence, and a bovine growth hormone polyadenylation sequence flanked by AAV2 inverted terminal repeats. The cDNA fragment was originally isolated from a human retinal cDNA library from unaffected individuals.

The timrepigene emparvovec drug product is formulated in a sterile, 20 mM Tris-buffered solution, pH 8.0, and contains 1 mM $MgCl_2$, 200 mM NaCl and 0.001% PF68. The drug product is a clear to slightly opalescent, colorless, sterile-filtered suspension with a target concentration of 1.0×10^12 vg/mL.

Timrepigene emparvovec will be administered in the study eye (i.e., the treated eye) as a sub-retinal injection following vitrectomy.

3.3 Study Schedule

At each study visit, an attempt should be made to perform all procedures/collect the data in both eyes, unless otherwise specified (Appendix 2: Schedule of Study Procedures).

A subject is considered to have completed the study if he completes the Month 12 assessments. The end of the study is the date the last subject completes his 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 Randomization

During the Screening/Baseline period, all subjects will be assigned a screening identifier, which will include the center number and subject number. If the subject fulfils all eligibility criteria during the Screening/Baseline period, a study eye will be assigned (prior to randomization) and the subject will be randomized in a 2:1:2 ratio to receive either timrepigene emparvovec high dose (1.0×10^11 vg), timrepigene emparvovec low dose (1.0×10^10 vg) or to enter the untreated Control group.

Randomization will be generated using a validated system that automates the random assignment of treatment groups and stratified by surgical group*. Once a subject is deemed

eligible, the investigative site (or authorized designee) will access the system, and the subject will be randomized using a standard blocked randomization.

Once a subject has been randomized, a change in "study eye" designation is not permitted.

At the time of randomization, a projected surgical date should be defined for each subject. For each subject randomized to the control group, this projected surgical date (+/- 1 day) should remain the Day 0 (Visit 2) date. For each subject randomized to a treated group, Day 0 will be the actual date of surgery.

All subjects' data (including screen failures) will be entered into the electronic case report form (eCRF).

* A surgical group will consist of a single 'Surgical Site' and 'Non-surgical Sites'. The Surgical Site will conduct baseline and follow-up visits for local subjects, as well as surgeries and immediate post-operative visits for all subjects treated in the surgical group. The 'Non-surgical Sites' will only perform the baseline/screening visit and the follow-up visits from Day 7 (Visit 4) onwards for their respective local subjects.

3.5 Study Masking

Randomization of subjects aims to minimize potential selection bias.

Given a double-masked design is not feasible (i.e. treatment involves invasive surgical procedure under general anesthesia), the sponsor, investigator and the subject will be unmasked to whether a subject has been assigned to the timrepigene emparvovec treatment groups, or the untreated Control group. However, within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^11 vg or 1.0×10^10 vg). To further minimize potential performance/detection bias, all subjective ophthalmic assessments at the Screening/Baseline Period (Visit 1) and from Month 1 (Visit 5) onwards, will be conducted by a masked (outcomes) assessor.

Additional measures to minimize potential performance/detection bias include standardized methodologies across participating sites (same equipment, assessor training/certification, surgical training), and an identical visit/assessment schedule for treated/untreated patients.

3.6 Sample Size

Approximately 160 subjects will be enrolled in the study (64, high dose group; 32, low dose group; 64, control group).

The sample size calculation is based on a Fischer's exact test. CHM is a degenerative disease, it is therefore assumed that a ≥15 letter BCVA gain would not be observed in subjects without CHM treatment. Assuming that 16.7% of the treated subjects will gain ≥15 letters BCVA at Month 12, 56 subjects in the high dose group and the control group provide at least 90% power at a 0.05 level of significance with a 2-sided test. To be conservative, 64 patients in the high dose group and 64 patients in the control group are needed to ensure 85% power in case 1 patient in the untreated control group has ≥15 letter BCVA gain by chance, which corresponds to a total of 160 patients completing the study.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion 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.

4.2 Key Secondary Efficacy Endpoints

There are 3 key secondary efficacy endpoints:

1. Change from Baseline in BCVA at Month 12 measured by the ETDRS chart
2. Proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12 measured by the ETDRS chart
3. Proportion 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

4.3 Other Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change from Baseline in BCVA at Months 4 and 8
- Change from Baseline in total area of preserved autofluorescence (AF) at Month 12
- Change from Baseline in the area of preserved ellipsoid zone (spectral domain optical coherence tomography [SD-OCT]) at Month 12
- Change from Baseline in microperimetry at Month 12
- Change from Baseline in contrast sensitivity score at Month 12
- Change from Baseline in colour vision at Month 12
- Change from Baseline in reading speed test at Month 12
- Change from Baseline in the 25-item Visual Function Questionnaire (VFQ-25) at Month 12

4.4 Exploratory Efficacy Endpoints

[redacted]

4.5 Safety Endpoints

The safety endpoints are:

- Overall adverse events (AEs), serious AEs (SAEs), and AEs (or SAEs) leading to discontinuations
- Clinical laboratory evaluations
- Vital signs including diastolic blood pressure, systolic blood pressure, and pulse

5 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

5.1 General Methods

All analyses and summaries will be produced using SAS® version 9.4 (or higher).

For descriptive summary statistics, the efficacy and safety data will be summarized and displayed by treatment groups (Control, Low Dose, High Dose) and visits (Baseline, Month 1, 4, 8, 12, and End of Study).

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. Where specified, the 95% Confidence Interval (CI) of the mean will be calculated. Summary statistics will be presented where appropriate by treatment and nominal visit with an additional entry for the end of study.

For categorical variables (including binary variables), counts and percentages will be presented. Where specified, the 95% 2-sided CI for proportions will be calculated.

The listings, except the listing for screen failures, will include all randomized subjects in the database. In general, the subject listings will be sorted by treatment group, subject number, eye (starting with the study eye) and assessment date (and time, if applicable).

Data for unscheduled assessments will be included when calculating baseline values, selecting worst result for shift analyses, and for summary of normal/abnormal values. The safety summary of observed and change from baseline data will be performed by nominal (i.e., scheduled) visits. Unscheduled visits will be included in the analysis of End of Study, i.e., the last available non-missing treatment endpoint.

5.2 Baseline Value

Baseline is defined as a value recorded at Visit 1 prior to treatment. Where this value is missing or unavailable, then an available Visit 2 (prior to treatment) result will be used.

- If there is more than one BCVA assessment, the median value will be used as baseline.
- If there is more than one microperimetry assessment, the most recent value will be used as baseline.

5.3 Study Day

Study day is defined as the number of days from the date of treatment (or phone contact for the untreated control group) to the event/visit date. It is calculated as follows:

If the event date falls on the date of treatment, or after the date of treatment then:

Study Day = Event or Visit Date – Treatment Date + 1

If the event date falls before the date of treatment then:

Study Day = Event or Visit Date – Treatment Date

5.4 Missing Data

If a subject discontinues the study prematurely, missing data handling will be specified in Section 5.5 and Section 10 EFFICACY ANALYSIS.

The AE and concomitant medication start/end dates will be imputed based on the rules described in Appendix 3.

5.5 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 accordance with the newly released FDA guidance 'Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency (June 2020)', alternative data ascertainment methods at an operational level are being explored such as using local non-study sites while international and interstate travel is limited due to COVID-19. In case an assessment is performed using the local non-study sites, subjects will be encouraged to attend their protocol-defined study sites for an ad-hoc visit (i.e., unscheduled visits) during which the per-protocol Month 12 assessments will be performed. Also, in line with the guidance, extension of the protocol-defined window aiming to include out-of-window visits is considered for performing the endpoint ascertainment. Data collected via these two approaches (assessment at local non-study sites, if applicable, as well as out of window visits) are further referred to as 'alternative data ascertainment'.

In terms of the statistical analysis, the impact of the COVID-19 pandemic on the STAR 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;
- Who had alternative data ascertainment at Month 12 due to COVID-19;
    - via the assessment at local non-study sites, if applicable
    - via the extension of out-of-window visits
- Who still missed their Month 12 visit due to COVID-19 despite the alternative data ascertainment.

The information for subjects who dies during the study and withdrew from the study due to COVID-19 will be recorded in the eCRF and the information for subjects who had alternative data ascertainment at Month 12 or missed their Month 12 visit due to COVID-19 will be documented as protocol deviation.

In addition, a summary table of COVID-19 related protocol deviation will be provided which contains the number (%) of subjects with at least one protocol deviation and the number (%) of subjects in each category for each study arm. The table will also present the summary statistics for major protocol deviations and important protocol deviations, respectively.

For subjects who missed the protocol-defined Month 12 BCVA assessment due to COVID-19, the following measures will be implemented. As a note, these data imputations and/or handling supersede any subsequent data imputation described in this document and will only be used for subjects and visits impacted by COVID-19.

- Both alternative data ascertainment (assessment at local non-study sites as well as out of window visits) will be included as primary analysis for all BCVA related endpoints, with details specified in the following bullets:
    - Where the Month 12 BCVA assessment is performed at local non-study sites with no further ad-hoc visit, the non-study site assessment is used as the Month 12 assessment in the primary analysis.
    - Where the Month 12 BCVA assessment is performed at local non-study sites with a further ad-hoc visit within 30 days from the assessment at non-study sites, the ad-hoc assessment is used as the Month 12 assessment in the primary analysis.
    - Where the Month 12 BCVA assessment is performed at local non-study sites with a further ad-hoc visit 31 days or more from the local non-study site assessment, the local non-study site assessment is used as the Month 12 assessment in the primary analysis.
- For subjects who withdraw from the study due to COVID-19, die during the study due to COVID-19, or fail to perform the Month 12 assessment despite the implemented alternative data ascertainment measures, the Month 12 assessment is considered as missing and missing data handling specified in Section 10 will be applied.

The rationale for including alternative data ascertainment, especially out of window visits in the primary analysis is the following: 1) It is in line with FDA and EMA guidance (U. S. Food and Drug Administration 2020, EMA 2020) on handling analysis during COVID-19 pandemic; 2) No further improvement in the treated patients is expected after the initial response around roughly 1-3 months, if any, post one-time injection of this gene therapy. Therefore, including the out of window visit, especially the visits beyond Month 12 scheduled window for the treated patients is considered a conservative approach considering potential trend of natural disease progression in the long-term follow up; 3) Very slow progression is expected in untreated control patients. The natural history study NIGHT showed an average of 0.5 letters of vision loss in untreated patients during 20 months follow up. Therefore, minimum impact on the analysis is expected from the usage of visits a few months post protocol defined window for the untreated patients, especially for the primary endpoint proportions of >= 15 letters increase from the baseline in BCVA.

Sensitivity analysis will be performed on the primary endpoint and the key secondary endpoints if applicable. The main analyses described in Section 10.1 and Section 10.2 will be repeated as follows:

- On the ITT population excluding subjects who withdraw from the study or died due to COVID-19 without any imputations, but include data collected by alternative ascertainment approaches.
- On the ITT population, where assessments performed at local non-study sites are replaced by the ad-hoc visit assessment (where available), irrespective of the interval between the ad-hoc visit and the local non-study site visit.
- On the ITT population, multiple imputation based on missing at random (MAR) will be applied to impute the data collected by alternative ascertainment approaches with Month 12 visit more than 2 months prior or 3 months after the protocol defined visit window or data missing from early termination or death due to COVID-19. In this

analysis, with extra scientific rigor, multiple imputation will also be applied to Month 12 BCVA collected more than 2 months prior or 3 months after the visit window not due to COVID-19. Assuming the BCVA at different visits follows a multivariate normal distribution, the Monte Carlo Markov Chain (MCMC) will be implemented to impute all missing data and the Month 12 BCVA collected more than 2 months prior or 3 months after the visit window (Schafer 1997, Schafer 1999). Each imputed data for continuous endpoint, analysis of covariance (ANCOVA) model including surgical group, baseline value of the assessment, and study arms will be applied. For binary endpoint, the proportion difference and the corresponding standard error between the treatment groups (i.e. high dose vs. placebo, low dose vs. placebo) will be calculated for each imputed dataset using the two-sample Binomial test. Analysis will be performed for each of the 100 imputed datasets and results will be combined by Rubin's rule (Rubin 1976, Rubin 1987) for inference assuming the statistics estimated from each imputed dataset are normally distributed. The Sample SAS code is in Appendix 4.

6 SUBJECT DISPOSITION

Subject disposition will be summarized for all screened subjects. Randomized subjects who complete the study or discontinue early from the study will be summarized by treatment group and overall subjects. The summary of subject disposition by discontinuation reason will also be presented. Within a treatment group or the overall summary, all percentages will be based on the number of randomized subjects within the treatment group or all randomized subjects, respectively.

A listing of study completion will be provided for all randomized subjects. A separate listing will be provided for screen failures with the reason for screen failure.

7 ANALYSIS POPULATION

7.1 Randomized Population

Randomized subjects will include all subjects whose date of randomization is not missing. The study population summary will be performed on the randomized subjects.

The randomized population will be used as supportive analysis for the primary and key secondary efficacy endpoints. Subjects will be analyzed based on the treatment to which they were randomized.

7.2 Safety Population

The safety population includes all subjects randomized either received study treatment [timrepigene emparvovec] or a post-randomization study visit (Telephone Call or a site visit) [Control].

Subjects will be analyzed according to their actual treatment received.

The safety population will be used for all safety analyses.

7.3 Intent-To-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects who are randomized, receive the study treatment (or the phone call for those in the untreated control group), and have at least one post-treatment BCVA measurement.

The ITT population will be used for the efficacy, quality of life, and [redacted]

The primary population for efficacy analysis is the ITT population. Subjects will be analyzed based on the treatment to which they were randomized.

7.4 Per Protocol Population

The Per Protocol (PP) population is a subset of the ITT population, whereby subjects with major protocol deviations that may affect substantially the results of the efficacy endpoints, are excluded. Subjects will be analyzed by randomized treatment. The definition of PP population is same as stated in the protocol, but an erratum of “actual treatment” is corrected in this document.

The determination of the major protocol deviations, and therefore the composition of the PP population, will be made prior to unmasking and will be documented and included in the analysis data.

The PP population will be used to analyze the primary and key secondary efficacy endpoints.

7.5 Immunogenicity Population

The Immunogenicity population will include all subjects from the safety population with at least one post-surgery sample evaluable for immunogenicity. The Immunogenicity population will be used for the immunogenicity analyses.

8 PROTOCOL DEVIATIONS

Protocol deviations will be collected during monitoring visits. Each instance of a protocol deviation will be reviewed by the Sponsor and determined to be either major or minor before data base lock (DBL).

The major protocol deviations with an impact on the analysis of the primary and key secondary endpoints could possibly include, but would not be limited to the following (to be finalized before DBL):

- Violated inclusion or exclusion criteria;
- Subject was unmasked;
- Subjects took a prohibited medication that is deemed per medical review to impact the assessment of efficacy or safety;
- Unmasked assessor performed ophthalmic assessments which should be conducted by masked observer.
- Subjects with Month 12 visit more than 2 months prior or 3 months after the protocol defined visit window.

Subjects with a major protocol deviation will not be included in the PP population.

Note as part of the STAR protocol, sites had to be EMMES certified for the assessment of visual acuity. At site [redacted], an issue that would compromise BCVA assessments below 34 ETDRS letters was noted. The findings of the EMMES certification at site [redacted] and the resulting impact assessment are described in detail in a separate document (STAR Site [redacted], EMMES Certification Assessment). In STAR, the inclusion criteria requiring a baseline BCVA between 34 and 73 ETDRS letters ensures that study eyes with a BCVA below 34 ETDRS letters would not be included into the study. However, it is possible that vision could have deteriorated to a level below 34 ETDRS letters during the conduct of the study due to the issue identified at site [redacted]. This could therefore potentially impact the evaluation of the primary and key secondary endpoints of BCVA evaluated at Month 12. Knowing the patients who had BCVA below 34 ETDRS letters at Month 12 for study eye will not be the responders for endpoints such as proportion of subjects with a ≥15-letter improvement from Baseline in BCVA at Month 12, proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12, those patients at site [redacted] with Month 12 BCVA below 34 ETDRS letters, if any, will be considered as minor protocol deviations, instead of major protocol deviations being excluded from the PP population. The handling these patients in primary and key secondary endpoints in per protocol analysis is detailed in Section 10.1 and Section 10.2.

A summary table will be provided which contains the number (%) of subjects with at least one protocol deviation and the number (%) of subjects in each category for each study arm. The table will also summarize the number (%) of subjects with a major protocol deviation and the number (%) of subjects with a major protocol deviation in each category. The table will also present the summary statistics for important protocol deviations. All protocol deviations will be listed.

9 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

9.1 Demographic and Other Baseline Characteristics

Demographics (sex, race, ethnicity, age [in years], age group [≤ 50 and > 50 years, ≤ 60 and > 60 years, ≤ median and > median years], baseline weight [kg]) will be summarized for the safety and ITT populations by treatment group and overall subjects. Sex, race, age group, and ethnicity will be summarized using summary statistics for categorical variables. Age and baseline weight will be summarized using summary statistics for continuous variables.

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 summarizing age. Where only the year of birth is reported as per local regulations, the date of birth will be assigned the value 30JUNYYYY.

A listing of demographic data will be provided for all randomized subjects.

9.2 Medical and Ocular History

9.2.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or higher. The number and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT), will be summarized by treatment. All percentages will be based on the number of subjects in the safety population within each treatment group. If a subject had a medical history term more than once, the subject will be counted only once under any given SOC or PT.

A listing of medical history will be provided for all randomized subjects.

9.2.2 Ocular History

Ocular History will be summarized by treatment and eye, by SOC and PT, for the safety population.

A listing of ocular history will be provided for all randomized subjects.

9.3 Prior and Concomitant Medications

All medications will be coded using the World Health Organization drug dictionary (WHODRUG) version March 1, 2018 or higher.

Incidence of prior and concomitant medication will be presented by treatment, Anatomical Therapeutic Chemical (ATC) Level 4 and PT for the safety population. Ocular medication will also be presented by eye (study eye and non-study eye).

Prior medications are those that start and stop before exposure to treatment; for control subjects, prior medications are defined as those with start and stop prior to Visit 2 (Day 0). Concomitant medications are all medications taken during the study period, including those started before but ongoing at the time of the injection (or Visit 2, Day 0 in the case of control subjects).

Imputation rules for partial dates are presented in Appendix 3.

A subject with more than one occurrence of the same medication in a particular ATC class will be counted only once in the total of those reporting medications in that particular ATC class.

Corticosteroid Treatment/Tapering will be summarized and listed separately.

9.4 Treatment Exposure

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

10 EFFICACY ANALYSIS

10.1 Primary Endpoint

The primary endpoint will be calculated as the proportion of subjects with a ≥15-letter increase from baseline in BCVA at the Month 12 visit. If a subject had BCVA missing at Month 12, the primary endpoint of the subject will be imputed as a failure.

The primary endpoint will be summarized using the summary statistics for categorical data including the 95% CI. The 95% CI for the difference in proportions will be computed using the method of Miettinen and Nurminen.

The primary endpoint will be compared between study arms (high dose vs control, low dose vs control) using the Fisher's Exact test. The primary approach will be the unstratified analysis, and a supportive analysis will be conducted with the Cochran-Mantel-Haenszel approach by stratifying by surgical group. As Fisher's Exact test is overly conservative when the number of events is low, a supportive analysis will be conducted using Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001 (Berger 1994). To maintain the test at 0.05 two-sided level, the reported p-value will be 2 times the one-sided p-value from the Fisher's Exact-Boschloo test.

The primary analysis of the primary endpoint will be based on the ITT population, and supportive analyses will be performed based on the PP population and the randomization population. Knowing the patients at site [redacted] who had BCVA below 34 ETDRS letters at Month 12 for study eye, if any, will not be the responders of subjects with a ≥15-letter improvement from Baseline in BCVA at Month 12, these subjects with minor protocol deviation will be included in the supportive analysis based on the PP population (see background information for site [redacted] in Section 8).

Let p_{high}, p_{low}, and p_{cont} represent proportions of subjects with an improvement (≥15-letter) from baseline in BCVA at Month 12 for treatments of high dose and low dose, and control group, respectively.

The following 2 hypotheses will be tested to compare the proportions between each treatment group (high dose or low dose) and control group at Month 12:

- High dose treatment versus control:
  - $H_{01}: p_{high} = p_{cont}$ versus $H_{11}: p_{high} \neq p_{cont}$
- Low dose treatment versus control:
  - $H_{02}: p_{low} = p_{cont}$ versus $H_{12}: p_{low} \neq p_{cont}$

Additional supportive analysis will be conducted by comparing the study eyes vs. the fellow eyes (i.e., contralateral control) within the low dose and the high dose treatment groups. The study eye will be compared to the fellow eye at the Month 12 visit using the paired McNemar test.

10.2 Key Secondary Endpoints

The three key secondary endpoints and the corresponding primary analysis are as summarized and presented by pre-specified order in Table 1.

The continuous efficacy endpoint will be analyzed by the analysis of covariance (ANCOVA) model including surgical group, baseline value of the assessment, and study arms. Missing data will be handled by the last observation carried forward (LOCF) approach.

The binary efficacy endpoints will be analyzed with the same method used for the primary efficacy endpoint with missing values imputed as failure.

The least square (LS) means, standard error (SE) and 95% CI will be reported for each treatment at each post-randomization visit. Least square mean, SE, 95% CI, and p-value for the between group differences will also be provided.

The primary analysis of the key secondary endpoints will be based on the ITT population, and supportive analyses will be performed based on the PP population and the randomized population. When performing the supportive analysis based on the randomized population, for subjects who do not have any post-baseline assessments, the baseline will be used when LOCF approach is applied (i.e. the change from baseline will be zero). Knowing the patients at site [redacted] who had BCVA below 34 ETDRS letters at Month 12 for study eye, if any, will not be the responders of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12, these subjects with minor protocol deviation will be included in the supportive analysis of the secondary endpoint of Proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12 measured by the ETDRS chart based on the PP population. When performing the supportive analysis based on PP population for the secondary endpoints of (a) Change from Baseline in BCVA at Month 12 measured by the ETDRS chart and (b) Proportion 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 ETDRS chart, subjects at site [redacted] who had BCVA below 34 at Month 12 will be excluded from these analyses. The background information for site [redacted] is described in Section 8.

Additional supportive analysis will be conducted by comparing the study eyes vs. the fellow eyes (i.e., contralateral control) within the low dose and the high dose treatment groups. The binary efficacy endpoints will be analyzed at the Month 12 visit using the paired McNemar test. Change from baseline in BCVA at Month 12 will be compared between the study eye and the fellow eye using the linear mixed model where the two eyes are considered correlated within each patient. The model will contain the variables for baseline BCVA, treatment groups (low dose and high dose), surgical group, eye (study eye vs fellow eye) and the treatment*eye interaction, where the eye variable acts as the repeat variable. (See sample SAS code in Appendix 5).

Table 1 Statistical Tests for Key Secondary Efficacy Endpoints

	Key Secondary Endpoint	Statistical Method
1	Change from Baseline in BCVA at Month 12 measured by the ETDRS chart	ANCOVA
2	Proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12 measured by the ETDRS chart	Fisher's Exact Test; Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001; CMH Approach
3	Proportion 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 ETDRS chart	Fisher's Exact Test; Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001; CMH Approach

Abbreviations: BCVA= best corrected visual acuity, CHM= choroideremia, ETDRS=Early Treatment of Diabetic Retinopathy Study

10.3 Multiplicity Adjustment

The protection of the type I error will be achieved for the comparison between the high dose and the untreated control under a hierarchical procedure. The primary efficacy endpoint will be first tested. If the p-value is <0.05, the study will be declared positive and the key secondary endpoints will be tested in the pre-specified order mentioned in Table 1. The comparison between the low-dose arm and the untreated control is considered as supportive and will be performed only if significance is achieved between the high dose and the untreated control on the same efficacy endpoint.

No multiplicity adjustment will be performed for the Data Monitoring Committee's (DMC) analysis of safety monitoring.

10.4 Sensitivity Analyses for Handling Missing Data

Sensitivity analyses will be performed based on the ITT population to evaluate the robustness of the primary and the key secondary endpoints and to assess the impact of missing data.

10.4.1 The Last Observation Carried Forward

For the binary endpoints, missing data will be handled by the LOCF approach.

10.4.2 Mixed Model Repeated Measures

For the change from baseline in BCVA, a mixed model repeated measures (MMRM) will be employed. The MMRM model will include treatment, visit (as a categorical variable), surgical group, baseline BCVA, treatment-by-visit interaction, and baseline BCVA-by-visit interaction.

An unstructured covariance matrix will be used for the within-subject correlation. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. In case of a convergence failure with the unstructured covariance, the following structures will be assessed in a sequential fashion until convergence is achieved: heterogeneous Toeplitz, Toeplitz, heterogeneous auto-regression, and auto-regression (See sample SAS code in Appendix 6).

10.4.3 Multiple Imputation Based on Missing Not at Random

For the change from baseline in BCVA, the pattern-mixture model using a control-based multiple imputation method will be performed based on missing data not at random for the ITT population. The method described here is based on methodology described by Little and Yau (1996) and extended in Ratitch and O'Kelly (2011). It assumes that subjects who discontinue from the study would have the same evolution of the disease as those subjects on the control group who remained in the study. The assumption that efficacy profiles of dropouts after discontinuation are similar to those of untreated control subjects is considered conservative because this methodology tends to minimize the difference between treatment and control groups. If the results of this analysis are in line with the primary efficacy results, then it can be confidently concluded that the primary analysis results are robust.

Using this method, missing data after discontinuation will be imputed based on control group data using multiple imputation methodology for all subjects (including treatment subjects).

The steps to implement this sensitivity analysis are as follows (See sample SAS code in Appendix 7):

1. 100 datasets will be generated where missing data at intermediate visit(s) will be imputed for each treatment group using non-missing data from all subjects within the treatment group by a Monte Carlo Markov Chain (MCMC) imputation model using the MCMC statement in the SAS PROC MI procedure. As a result, each dataset will only have missing ending data, or a monotone missing data pattern.
2. For each dataset from Step 1, missing ending data will be imputed based on information from the control group. As a result, 100 imputed complete datasets will be generated.
    - Missing data at the first post-baseline visit will be imputed by a regression imputation model using the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.
    - The SAS PROC MI procedure will use data from all control subjects as well as treatment subjects with missing data at the visit (i.e., only those that need imputation at the visit). Because subjects from treatment groups without missing data at the visit are excluded from this step, they will not contribute to the estimation of the imputation model for the visit.
    - The same process will be used for all other visits. Subjects whose missing data were imputed at previous visits will contribute to the imputation for the next visit.
    - The regression imputation model includes an intercept and the slopes of the measurements from all previous visits.
3. Analyze each imputed complete dataset.
4. Combine estimates from the results of each model.

10.5 Other Secondary Efficacy Endpoints

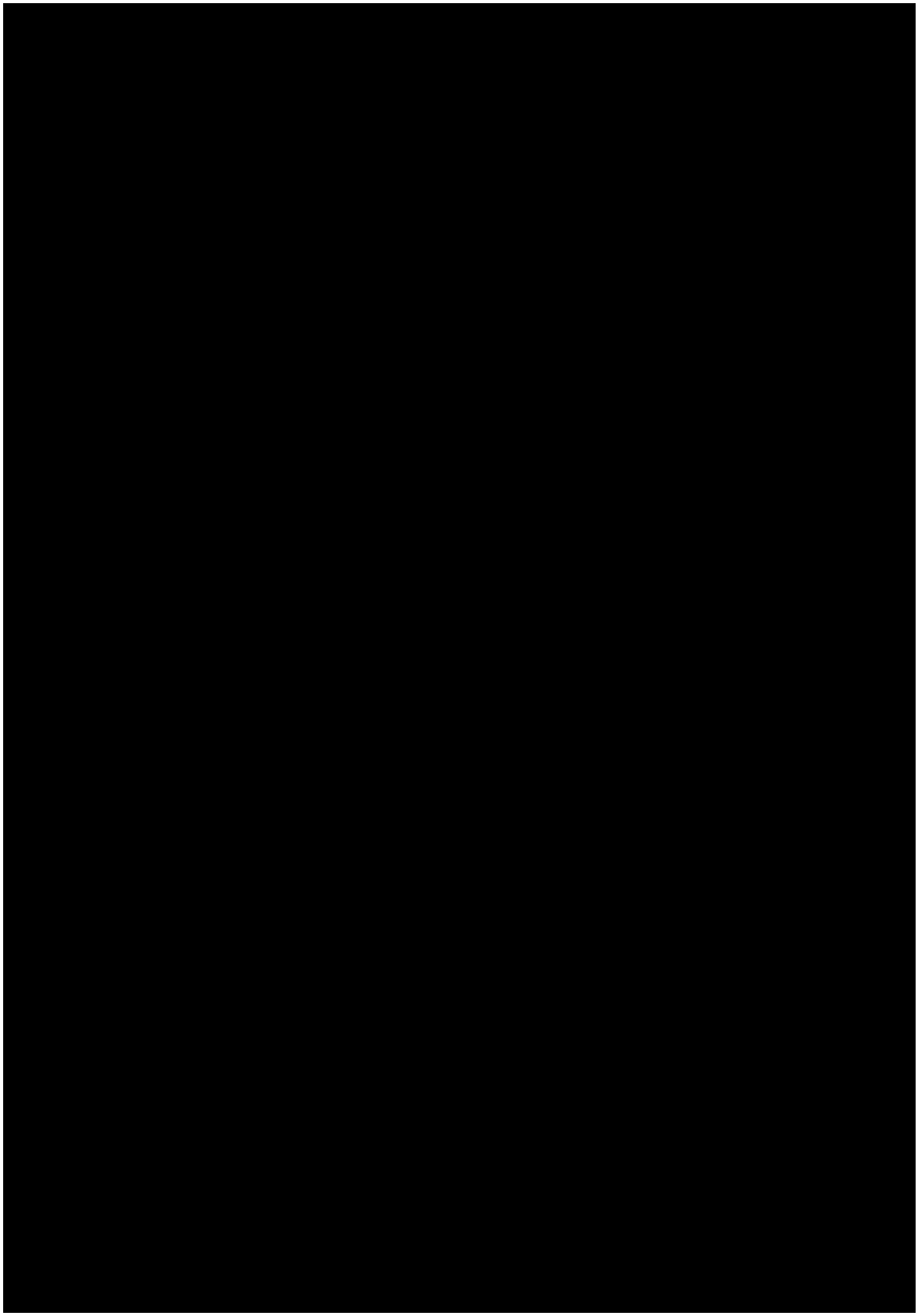
For the analysis of the following efficacy endpoints, the same analysis of covariance (ANCOVA) model will be utilized based on the ITT population with missing data handled by the LOCF approach.

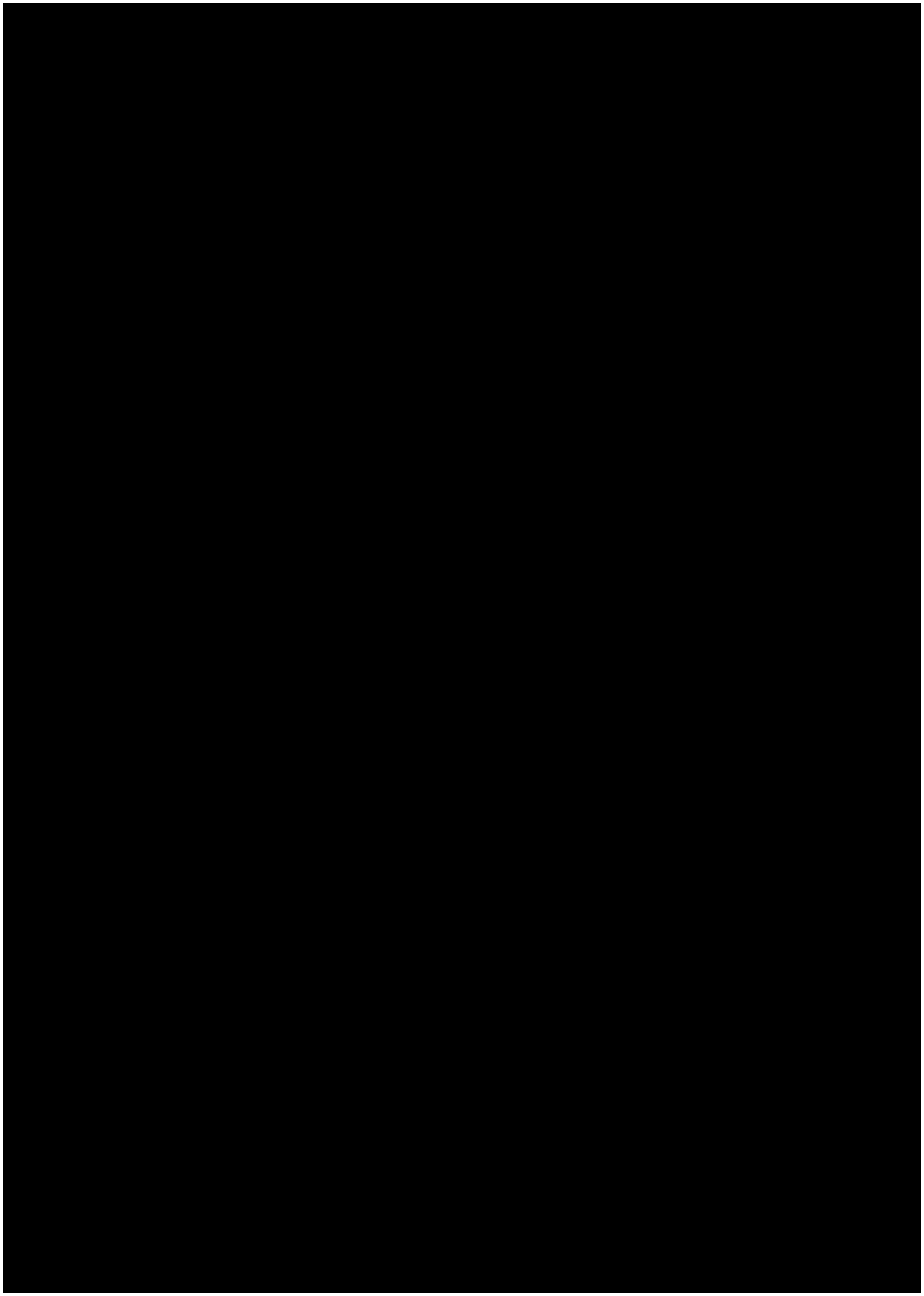
- Change from Baseline in BCVA at Months 4, 8 and 12
- Change from Baseline at Month 12 in:
    - Total Area of Preserved AF
    - Distance from Foveal Center (FC) to nearest Border of Preserved AF
- Change from Baseline in the following SD-OCT variables at Month 12:
    - Foveal Subfield Thickness
    - Total Macular Volume
    - Central Horizontal Ellipsoid Width

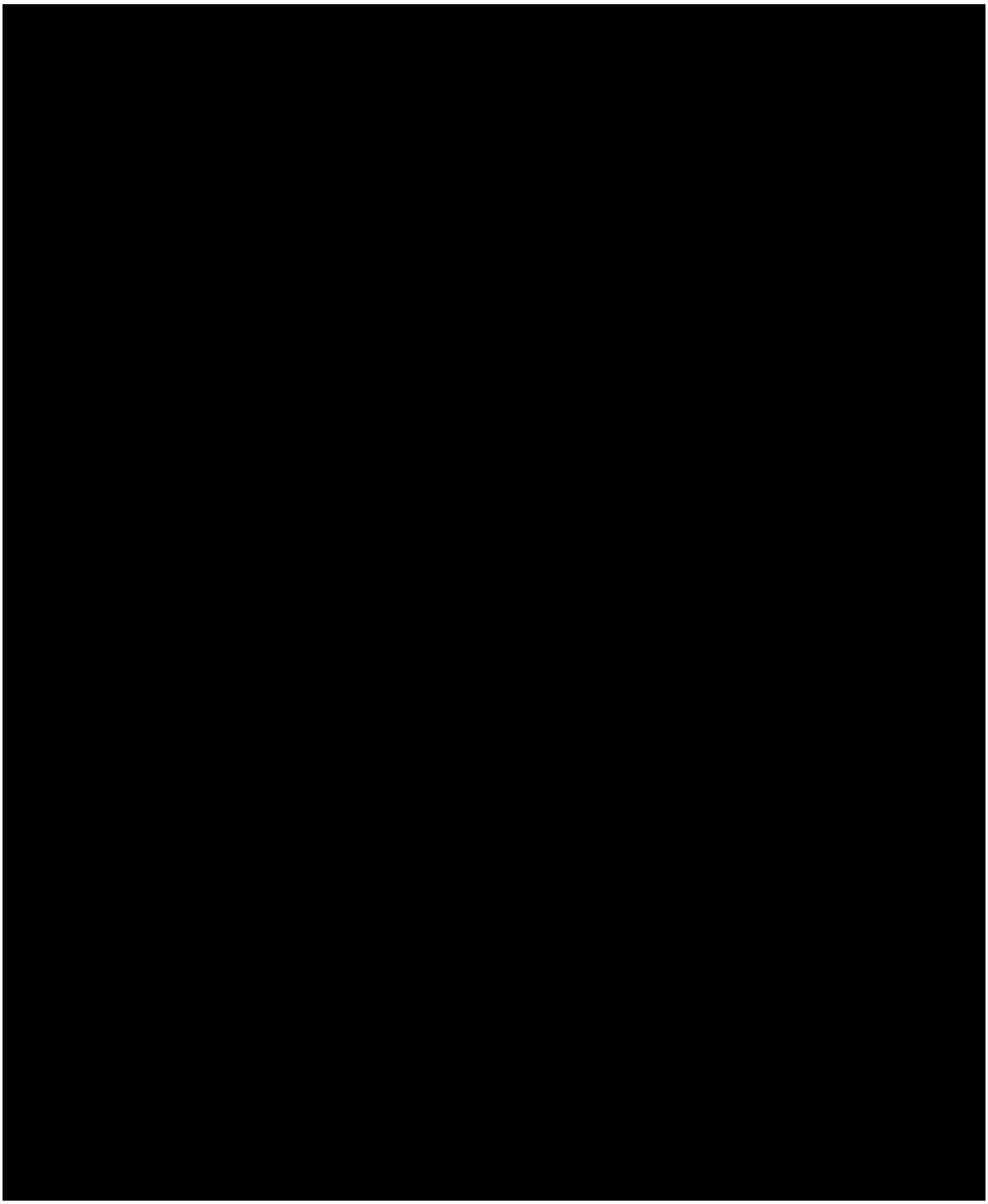
  - Central Ellipsoid Area
  - Choroidal Thickness
- Change from Baseline in the following microperimetry variables at Month 12:
  - Mean Sensitivity
  - Bivariate Contour Ellipse Area 63%
  - Bivariate Contour Ellipse Area 95%
- Change from Baseline in contrast sensitivity score at Month 12
- Change from Baseline in colour vision at Month 12
- Change from Baseline in reading speed test at Month 12
  - The reading speed will be calculated using the following formula: [number of words in the text - number of misread words] / reading time x 60. The number of words per text is available in Appendix 1: IRest Reading Speed Test, Conversion Table, while the number of misread words and reading time will be collected in the case report form (CRF).
- Change from Baseline in the 25-item VFQ-25 overall score and sub-scale scores at Month 12
  - The VFQ-25 patient questionnaire consists of 25 vision-related questions, each of them pertaining to one of the 11 vision-related subscales. For each subscale, a score is calculated. Scores are between 0 and 100, where a higher value represents better functioning. The overall composite score is calculated as the mean of the sub-scale scores (Mangione 2000).

10.6 Exploratory Analysis

[redacted]







11 SAFETY ANALYSIS

All analyses of safety data will be performed using the safety population. All analyses of safety data will be presented using descriptive summary text. No inferential analyses of safety data will be needed.

11.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as adverse events starting on or after the day of the surgery (or, for control subjects, Visit 2, Day 0). A pre-existing event that worsens in severity after Day 0 is treated as a new TEAE with date of onset set to the date of the increased severity. Summary tables will include TEAEs only. TEAEs will be summarized by eye (study eye vs non-study eye) for ocular events, by treatment (low dose, high dose and untreated control) and overall. Non-treatment emergent AEs will be listed only.

An ocular event is an event where the site of the event is reported as both eyes (OU), right eye (OD) or left eye (OS).

Proportion of subjects reporting an event will be calculated based on the number of subjects in the corresponding treatment group. The 95% CI will be calculated using the Clopper-Pearson method.

The number and percentage of subjects reporting any event, any non-ocular event, any ocular event, any ocular event in the study eye and any ocular event in the non-study eye will be summarized.

The summary of overall AEs (or SAEs) will be limited to TEAEs. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or higher.

An overall summary table of TEAE by treatment will be provided for the following categories:

- Number and percentage of subjects with a TEAE
- Number and percentage of subjects with a treatment-related TEAE
- Number and percentage of subjects with a serious TEAE
- Number and percentage of subjects with a treatment-related 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 treatment group and overall for subjects in the safety population. The following summaries of TEAEs will be provided:

- TEAEs by SOC and PT
- TEAEs by SOC and PT reported in ≥ 5% in any treatment group

- TEAEs by SOC, PT, and maximum severity (missing severity, if any, will be counted as severe).
- 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
- 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
- TEAE leading to death by SOC and PT

In the summary, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. 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 (related to Study Drug, related to Study Procedure, related to both 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.

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 separated document (BIIB111 Signal Detection Plan). The following summaries will be provided by treatment:

- 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 3.

Summaries presenting frequency of AEs by SOC and PT will be ordered by descending frequency of SOC in the High Dose group and then, within a SOC, by descending frequency of PT in the High Dose group.

The following listings will be provided:

- All AEs
- AEs reported by subjects who discontinued from the study due to an AE
- All SAEs

- AEs leading to death

11.2 Vital Signs

Blood pressure, pulse and change from baseline will be summarized by visit and by treatment.

11.3 Intraocular Pressure

Intraocular pressure and change from baseline will be summarized by visit and by treatment.

11.4 Slit Lamp Examination Outcomes

The number and percentage of subjects within each category of slit lamp examinations outcomes will be summarized by visit, by eye and by treatment. 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 follow:

- 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 follow:

- 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).

11.5 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 summarized by visit, by eye and by treatment. Shift from baseline will also be evaluated.

The categories for lens opacity grades are defined as Category 1, 2, 3 and 4.

The categories for the Shift from baseline are defined as follow:

- 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

11.6 Dilated Ophthalmoscopy Outcomes

The number and percentage of subjects within each category of each dilated ophthalmoscopy outcomes will be summarized by visit, by eye and by treatment. 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 follow:

- 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 follow:

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

11.7 Fundus Photography

Presence and severity of retinal pigment epithelium (RPE) hyperplasia, retinal arteriolar narrowing, retinal vessel sheathing, optic atrophy/pallor and optic disc swelling and presence of TOF will be analysed.

The categories for the Shift from Baseline are defined as follow:

- 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.

The images quality will be summarized by visit and eye, by treatment and overall, based on counts and percentages. This includes image completeness, focus/clarity, field definition, stereopsis, exposure and contrast.

11.8 Immunogenicity Findings

Immunogenicity analyses will be performed on the Immunogenicity Population. Three immunogenicity assays will be analyzed: Anti-Drug Antibodies (ADA), Neutralizing timrepigene emparvovec antibodies (Nabs) and ELISpot.

In ELISpot data, a subject will be tested by 4 different analytes (REP1 Pool 1, REP1 Pool 2, REP2 Pool 3, AAV2) at each visit. All 4 analytes together are used to evaluate the immune response of the whole therapeutical product of BIIB111, in which, the 3 REP1 analytes are used to evaluate the immune response of the therapeutical gene, and the AAV2 analyte is used to evaluate the immune response of the transporting gene. A subject will be determined to have a positive result if any of the 4 analytes is positive at that visit. A subject will be determined to have a positive result with respect to the REP1 if any of the 3 REP1 analyte is positive at that visit. A subject will be determined to have a positive result with respect to the AAV2 if the AVV2 analyte is positive at that visit.

Baseline Definition

The baseline value for the immunogenicity assays is defined as the last available value prior to surgery of the study eye (or the study visit 2 Telephone Call for Control subjects). For subjects without any assessments prior to surgery of the study eye (low dose and high dose treatment groups), Day 1 sample will be used as baseline.

Assay Positivity by Visit

The number and percentage of subjects with positive results at any visit will be presented by baseline status (positive/negative) and by treatment group. Samples with a numeric titre is considered as positive. The positivity analysis for ELISpot will be summarized for the overall treatment of BIIB111 as well as with respect to either REP1 or AAV2.

Assay Treatment-Emergent Analysis by Visit

The number and percentage of subjects with a treatment-emergent positive result will be presented by visit and by treatment group. 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.

A treatment-emergent positive result is defined as follow 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. If either REP1 or AAV2 is treatment-emergent positive, it is a treatment-emergent positive for the overall treatment of BIIB111.

If either 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 post-baseline assessments will be tabulated and will contribute to the positive/negative overtime summary. Invalid sample results include, but are not limited to "Quantify Not Sufficient", "No Results", "Pending Reassay Selection".

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 baseline and subjects with positive assay at baseline; and (2) subjects with at least one treatment-emergent positive assay at any visit during the study and subjects with no treatment-emergent positive assay during the study. For ELISpot, the relationship with the selected adverse events will be summarized for the overall treatment of BIIB111 as well as with respect to either REP1 or AAV2.

The analyses will be conducted by treatment group and by eye. 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.

Listings

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.

12 SUBGROUP ANALYSIS

The primary and key secondary efficacy endpoints along with the [redacted] will be summarized by the following subgroups in Table 2.

Table 2 Subgroups Defined at Baseline

Subgroup	Values
Age group 1	≤ median age > median age
Age group 2	≤ 40 years old > 40 years old
Race	White Non-white (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander)
Region	America Europe
Ethnicity	Hispanic or Latino Not Hispanic or Latino
Surgical group	Each of the surgical groups
Baseline BCVA	≤ median baseline BCVA > median baseline BCVA
Microperimetry mean sensitivity	≤ median baseline mean sensitivity > median baseline mean sensitivity
Microperimetry fixation	Unstable/relatively unstable Stable
Location of preserved autofluorescence on FAF	Non-subfoveal Subfoveal
ADA	Positive Negative
Nab	Positive Negative
ELISpot (overall treatment of BIIB111)	Positive Negative

13 DROP OUT PROFILE

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

The pattern of missing data due to discontinuation will be characterised by summarising the time to discontinuation based on the Kaplan-Meier estimates and the corresponding Kaplan-Meier curves. Time to discontinuation is calculated as the date of discontinuation – date of Visit 2 (i.e., surgery or phone contact) + 1.

14 APPENDICES

14.1 Appendix 1: IRest Reading Speed Test, Conversion Table

Language	Text	Number of Words
English	1 – Mice	156
	2 – Beaver	161
	3 – Trees	156
	4 – Prey	165
	5 – Desert	155
	6 – Venom	136
	7 – Island	158
	8 – Spiders	159
	9 – Winter	148
	10 – Colors	141
German	1 – Mäuse	132
	2 – Biber	137
	3 – Bäume	131
	4 – Beute	138
	5 – Wuste	133
	6 – Gift	129
	7 – Inseln	130
	8 – Spinnen	130
	9 – Winter	133
	10 – Farbe	129
Dutch	1 – Muizen	141
	2 – Bever	147
	3 – Bomen	139
	4 – Buit	146
	5 – Woestijnen	138
	6 – Gif	141
	7 – Eilanden	146
	8 – Spinnen	140
	9 – Winter	138
	10 – Kleur	138
Finnish	1 – Hiiret	100
	2 – Majava	104
	3 – Puut	102
	4 – Saalis	104
	5 – Aavikko	105
	6 – Myrkky	102
	7 – Saaret	107
	8 – Hämähäkit	99
	9 – Talvi	94
	10 – Värit	98

14.2 Appendix 2: Schedule of Study Procedures

Visit	Visit 1[a]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[a]	Visit 6[a]	Visit 7[a]	Visit 8[a, c]	Early Termination[d]	Unscheduled Visit[e]
Study Day/Visit Window	**Screening/ Baseline[f]**	**Day 0 *Injection Day***	**Day 1 *Post op***	**Day 7 *Post op* ± 3d**	**Month 1 ± 7d**	**Month 4 ± 7d**	**Month 8 ± 14d**	**Month 12 ± 14d**		
Informed Consent	X									
Demographics, medical and ocular history	X									
Immunoassay blood sampling (ELISA and cell-based methods)[g]	X		X	X	X	X	X	X	X	
Immunoassay blood sampling (ELISPOT)[g]	X		X	X	X	X	X	X	X	
VFQ-25[h]	X							X	X	
Vital Signs	X		X	X	X			X	X	
Weight[i]	X									
[redacted]										
BCVA[k]	X		X	X	X	X	X	X	X	X
Full ophthalmic exam[l]	X	X	X	X	X	X	X	X	X	X
SD-OCT	X		X	X	X	X	X	X	X	X
Autofluorescence	X			X	X	X	X	X	X	X
Microperimetry	X				X	X	X	X	X	
Contrast sensitivity[m]	X					X	X	X	X	
Colour vision	X					X	X	X	X	
7-field colour fundus photos[n]	X							X	X	
Reading speed test[o]	X							X	X	
Randomisation	X									
Corticosteroid dispensation/accountability[p]	X	X	X	X	X					

Visit	Visit 1[a]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[a]	Visit 6[a]	Visit 7[a]	Visit 8[a, c]	Early Termination[d]	Unscheduled Visit[e]
Study Day/Visit Window	**Screening/ Baseline[f]**	**Day 0 *Injection Day***	**Day 1 *Post op***	**Day 7 *Post op* ± 3d**	**Month 1 ± 7d**	**Month 4 ± 7d**	**Month 8 ± 14d**	**Month 12 ± 14d**		
Study drug/sub-retinal injection/vitrectomy/ retinal detachment		X[r]								
AE/SAE monitoring[q]	X	X	X	X	X	X	X	X	X	X
Concomitant medication, procedures and treatment review	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; BCVA=best corrected visual acuity; ELISA=enzyme-linked immunosorbent assay: ELISPOT=enzyme-linked immunospot; ET=early termination; IOP=intraocular pressure; [redacted]; SAE=serious adverse event; SD-OCT=spectral domain optical coherence tomography; VFQ-25=25-item Visual Function Questionnaire.

NOTE: An attempt should be made to perform all procedures in both eyes, unless otherwise specified. Each eye should be tested separately. If the subject is unable to complete a procedure due to poor vision in either eye, this should be documented in the source notes and the assessment not completed for that eye.

Assessments with gray shading are to be assessor-masked.

[a] Visit may be performed over 2 consecutive days if necessary.

[b] Study Visits 2, 3, and 4 only apply to subjects in the AAV2-REP1 groups. For subjects in the Control group, a telephone contact will be made at Visits 2, 3, and 4, and information regarding AEs/SAEs and concomitant medications, procedures, and treatments will be recorded.

[c] End of Study Visit.

[d] An ET visit should 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, all assessments listed will be performed.

[f] Informed consent must be signed within 12 weeks prior of dosing (Visit 2). The Screening/Baseline Visit must be performed within 8 weeks of dosing (Visit 2). Assessments and procedures conducted in the final visit of the NIGHT study (including the ET Visit) may be used for the Screening/Baseline Visit if the final NIGHT study occurs within 8 weeks prior to dosing (Visit 2).

[g] Samples will be taken and retained for analyses, if necessary.

[h] VFQ-25: to be completed only at sites where a validated translation is available. VFQ-25 must be completed by subjects at the beginning of the study visit, before any significant interaction with the study staff.

[i] Weight is assessed for dose calculation for 21-day corticosteroid regimen.

[redacted]

[k] In order to capture accurate BCVA values at Visit 1 (Screening/Baseline), the following conditions apply to the BCVA assessment:

If the BCVA value at Visit 1 (Screening/Baseline) is ≥ ±10 letter gain or loss in the study eye compared to the previous NIGHT study visit (if applicable), then BCVA must be repeated an additional 2 times, resulting in a total of 3 BCVA measures at Visit 1. To facilitate the additional BCVA measures this visit should be conducted over 2 days, with BCVA measured twice on Day 1 and once on Day 2. All 3 BCVA values must be recorded in the eCRF. The highest score will be used to define subject eligibility.

If the BCVA value at Visit 1 (Screening/Baseline) is < ± 10-letter difference in the study eye compared to the previous NIGHT study visit (if applicable), then BCVA will be collected once and will not be repeated.

If the subject was not previously in the NIGHT study, BCVA assessments at baseline must be performed in triplicate over a period of 2 days, as described above. At least 2 of the triplicate values must meet BCVA eligibility requirements for inclusion in the study and the difference between the 3 assessments may not be ≥ 10 letters.

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

[m] Pelli Robson chart will be used for contrast sensitivity.

[n] Stereo photos for Fields 1, 2, 3.

[o] International Reading Speed Texts. To be completed only in languages for which a validated translation is available.

[p] For AAV2-REP1-treated subjects, only: corticosteroid (prednisone/prednisolone) will be dispensed at Visit 1 or at least 2 days prior to Visit 2 with instruction to start treatment 2 days before the planned surgical date, and to continue for 21 days in total.

[q] AEs/SAEs will be collected from the time the subject provides written informed consent through the End of Study Visit (or ET Visit or Unscheduled Visits, if applicable).

[r] For subjects in the AAV2-REP1 groups only. On the Injection Day Visit (Visit 2, Day 0), all subjects in the AAV2-REP1 groups will undergo vitrectomy and treatment with AAV2-REP1.

14.3 Appendix 3: 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.

14.4 Appendix 4. Multiple Imputation based on MAR – Sample SAS Code

```
*** make the data monotone missing ***;
PROC MI DATA=dset OUT=dset1 NIMPUTE=100 SEED=1234;
BY TRT;
VAR BASELINE VISIT2 VISIT3 VISIT4 VISIT5 VISIT6;
MCMC chain=multiple impute=monotone;
RUN;

*** impute to impute missing data ***;
PROC MI data=dset1 seed=1234 nimpute=1 out=dsetall;
CLASS TRT;
VAR TRT BASELINE VISIT2 VISIT3 VISIT4 VISIT5 VISIT6;
Monotone reg(VISIT2=TRT BASELINE /details);
Monotone reg(VISIT3=TRT BASELINE VISIT2/details);
Monotone reg(VISIT4=TRT BASELINE VISIT2 VISIT3 /details);
Monotone reg(VISIT5=TRT BASELINE VISIT2 VISIT3 VISIT4/details);
Monotone reg(VISIT6=TRT BASELINE VISIT2 VISIT3 VISIT4 VISIT5/details);
RUN;
```

14.4.1 Continuous endpoint

```
*** Analyze the continuous data on the last timepoint by ANCOVA ***;
PROC MIXED data=dsetall;
BY _IMPUTATION_;
CLASS TRT;
MODEL CHG=BASELINE TRT;
LSMEANS TRT / PDIFF CL;
ESTIMATE "High vs Control" TRT 1 0 -1;
ESTIMATE "Low vs Control" TRT 0 1 -1;
          ODS OUTPUT LSMEANS=LSMEAN;
          ODS OUTPUT ESTIMATES=LSEST;
RUN;

*** Use Rubin's Rule ***;
PROC MIANALYZE parms=lsest;
BY LABEL;
MODELEFFECTS ALLEST;
ODS OUTPUT PARAMETERESTIMATES=PARMS;
RUN;
```

14.4.2 Binary endpoint

```
/*** compute the proportion difference and the corresponding standard error between
the treatment groups (i.e. high dose vs. placebo, low dose vs. placebo) for each
imputed dataset. Use Rubin's Rule to combine the results ***/

PROC MIANALYZE data=propest;
modeleffects prop_diff;
stderr se_diff;
ods output parameterestimates = PARMS;
run;
```

14.5 Appendix 5: Linear Mixed Model for Study Eye vs Fellow Eye Comparison – Sample SAS Code

```
PROC MIXED DATA=dset; /* assumes data presented in rows */
  CLASS trt eye subject;
  /* be careful of the sequences of the variable here */
  /* see notes later */
  MODEL var_chg= eye trt eye*trt var_bl/ DDFM=KENWARDROGER;
  REPEATED eye / SUBJECT=subject TYPE=UN R RCORR RI;
  LSMEANS eye*trt;
  ESTIMATE 'high dose: study eye vs fellow eye' eye 1 -1 eye*trt 1 -1 0 0 0 0;
  ESTIMATE 'low dose: study eye vs fellow eye'  eye 1 -1 eye*trt 0 0 1 -1 0 0;
  ESTIMATE 'control: study eye vs fellow eye'   eye 1 -1 eye*trt 0 0 0 0 1 -1;

/* the variable 'eye' indicates whether the data are study eye or fellow eye   */
/* 1 is associated to the study eye data                                       */
/* -1 is associated to the fellow eye data                                     */
/* treatment is coded as 1-high dose, 2-low dose, 0-control                    */
/* note the sequence of variables in the CLASS statement is very tricky        */
/* in order for the ESTIMATE statement to work correctly:                      */
/* if it appears in CLASS statement as 'eye trt subject', then the ESTIMATE    */
/* statement has to be, for example,                                           */
/* ESTIMATE 'high dose:study eye vs fellow eye' eye 1 -1 eye*trt 1 0 0 -1 0 0; */
/* When interaction term is added, this statement must be modified             */

  RUN;
```

14.6 Appendix 6: Mixed Model Repeated Measures – Sample SAS Code

```
PROC MIXED DATA=dset;
CLASS subject surgsite study trt VISIT;
/* the order of variables in class statement here needs to match       */
/* with the ESTIMATE statement later                                   */
MODEL VA = blbcva surgsite study VISIT trt VISIT*trt BLBCVA*VISIT
               / DDFM=KENWARDROGER S;
REPEATED / TYPE=UN SUBJECT=subject R;
LSMEANS visit*trt;
ESTIMATE 'month 12: high dose vs control'
            trt 1 0 -1 trt*visit 0 0 0 0 1 0 0 0 0 0 0 0 0 0 -1;
            /* assume 5 visits in total here */
ESTIMATE 'MONTH 12: LOW DOSE VS CONTROL '
            trt 0 1 -1 trt*visit 0 0 0 0 0 0 0 0 0 1 0 0 0 0 -1;
            /* assume 5 visits in total here */
RUN;
```

14.7 Appendix 7: Multiple Imputation based on MNAR – Sample SAS Code

```
*** make the data monotone missing ***;
PROC MI DATA=dset OUT=dset1 NIMPUTE=100 SEED=1234;
BY TRT;
VAR BASELINE VISIT2 VISIT3 VISIT4 VISIT5 VISIT6;
MCMC chain=multiple impute=monotone;
RUN;

*** for control arm, use all available data to impute missing data ***;
PROC MI DATA=dset1(where=(TRT='Placebo')) out=dset2 nimpute=1 seed=1235;
BY _IMPUTATION_;
VAR BASELINE VISIT2 VISIT3 VISIT4 VISIT5 VISIT6;
MONOTONE REG(VISIT2=BASELINE/details);
MONOTONE REG(VISIT3=BASELINE VISIT2/details);
MONOTONE REG(VISIT4=BASELINE VISIT2 VISIT3/details);
MONOTONE REG(VISIT5=BASELINE VISIT2 VISIT3 VISIT4/details);
MONOTONE REG(VISIT6=BASELINE VISIT2 VISIT3 VISIT4 VISIT5/details);
RUN;

*** for active arm, impute missing data on VISIT2 using control arm ***;
PROC MI DATA=dset1(where=((TRT='Active' and VISIT2=.) or (TRT='Placebo' and
VISIT2>.))) out=dset3 nimpute=1 seed=1235;
BY _IMPUTATION_;
VAR BASELINE VISIT2;
MONOTONE REG(VISIT2=BASELINE/details);
RUN;


*** for active arm, impute missing data on VISIT3 using control arm ***;
PROC MI DATA=dset3(where=((TRT='Active' and VISIT3=.) or (TRT='Placebo' and
VISIT3>.))) out=dset4 nimpute=1 seed=1235;
BY _IMPUTATION_;
VAR BASELINE VISIT2 VISIT3;
MONOTONE REG(VISIT3=BASELINE VISIT2/details);
RUN;

*** repeat the same method for each sequential visit in active arm ***;

*** set all data together ***;
*** DSETX is the subset of active subjects with missing on VISIT2 ***;
*** DSETY is the subset of active subjects without missing on VISIT2 ***;
Data dsetall;
Set dset2 dsetX dsetY;
RUN;

*** Analyze the data on the last timepoint by ANCOVA ***;
PROC MIXED data=dsetall;
BY _IMPUTATION_;
CLASS TRT;
MODEL CHG=BASELINE TRT;
LSMEANS TRT / PDIFF CL;
ESTIMATE "High vs Control" TRT 1 0 -1;
ESTIMATE "Low vs Control" TRT 0 1 -1;
ODS OUTPUT LSMEANS=LSMEAN;
ODS OUTPUT ESTIMATES=LSEST;
RUN;

*** Use Rubin's Rule ***;
PROC MIANALYZE parms=lsest;
BY LABEL;
MODELEFFECTS ALLEST;
ODS OUTPUT PARAMETERESTIMATES=PARMS;
RUN;
```

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