COVER PAGE

Official Title:	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)
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Study Indication:	Choroideremia

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1. SYNOPSIS CLINICAL STUDY REPORT

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Name of Finished Product:	**Name of Active Ingredient:**	**Study Indication:**
Timrepigene emparvovec	AAV2-REP1 (BIIB111)	Choroideremia

Title of Study:

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)

Principal Investigator/Coordinating Investigator:

The Coordinating Investigator's signature indicating approval of this report is provided in Appendix 16.1.5.

The approval of the Sponsor's Responsible Signatory is also provided in Appendix 16.1.5.

Study Period:	**Phase of Development:** 2
Date of first treatment: 29 November 2017 End of study date: 29 June 2022	

Study Objective:

The objective of the study was to evaluate the safety of bilateral, sequential, subretinal administration of a single dose of adeno-associated viral vector serotype 2 encoding rab escort protein 1 (AAV2-REP1) in adult male participants with choroideremia (CHM).

Study Design:

This was a multicenter, open-label, prospective, 2-period, bilateral, interventional safety study of AAV2-REP1 in adult male participants with genetically confirmed CHM. The study consisted of a Screening Period followed by 2 treatment periods (study eye 1 [SE1] treated in Period 1 and study eye 2 [SE2] treated in Period 2).

After undergoing a standard vitrectomy and retinal detachment, participants received a subretinal injection of up to 0.1 mL of study drug containing 1×10^{11} AAV2-REP1 vector genome (vg) for each eye (Period 1 Day 0 corresponded to the injection day visit for SE1, and Period 2 Day 0 corresponded to the injection day visit for SE2). Administration of study treatment in each eye was separated by an observational period. Each study eye was followed for at least 12 months post-treatment, for up to 9 visits per treatment period.

The estimated target interval between the surgical procedures of SE1 and SE2 was determined at the Screening Visit. Participants were treated with a short (< 6 months), medium (6-12 months), or long (> 12 months) surgery window between treatment of the first and second eyes. Because the timing of the second surgery visit (Period 2, Visit 1) varied among participants, the duration of Period 1 was also variable.

Participants were assessed for safety and efficacy throughout the study. Participants who developed cataracts underwent cataract surgery if deemed clinically necessary; if surgery was performed, it was carried out at least 4 weeks before Month 12 for the respective eye.

Participants who had previously participated in a clinical trial of AAV2-REP1 for the treatment of CHM and had received AAV2-REP1 in 1 eye were eligible for participation in this study for treatment in the untreated eye (participants were moved directly to Period 2 for treatment of SE2).

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To minimize inflammation resulting from surgery, and potential or unexpected immune responses to the vector/transgene, all participants received a course of oral prednisone/prednisolone, initiated 2 days prior to surgery on both SE1 and SE2.

For participants who received treatment with AAV2-REP1 in a previous study, biological samples had to be available to obtain an adequate immunogenicity profile related to treatment. These participants required Sponsor approval before being enrolled into this study.

Additional details are available in the protocol (Appendix 16.1.1, Protocol NSR-REP-02 [273CH203]), Version 6.0, Section 7.1).

Number of Subjects (Planned and Analyzed):

Planned: Approximately 60 participants were planned for the study.

Analyzed: A total of 82 participants were screened, 66 participants received study treatment, and 16 participants were screen failures; 53 participants completed the study.

Study Population:

Main Inclusion Criteria:

- Male ≥ 18 years of age
- Documented genetically confirmed diagnosis of CHM.
- Active disease clinically visible within the macular region of both eyes.
- Best corrected visual acuity (BCVA) of ≥ 34 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (20/200 or better Snellen acuity) in both eyes, or in the untreated eye, if the other eye was previously treated with AAV2-REP1.

Main Exclusion Criteria:

- History of amblyopia or inflammatory disorder in either eye.
- Unwilling to use barrier contraception methods or abstain from sexual intercourse for a period of 3 months following treatment with AAV2-REP1 in either eye.
- Previous intraocular surgery performed within 3 months of the Screening Visit in either eye.
- Any other significant ocular or nonocular disease/disorder which, in the opinion of the Patient Eligibility Review Committee or Investigator, may have either put the participant at risk because of participation in the study, or may have influenced the results of the study or the participants' ability to participate in the study. This included but was not limited to:
  - a contraindication to oral corticosteroid (e.g., prednisolone/prednisone)
  - a clinically significant cataract in either eye
  - not an appropriate candidate for subretinal surgery
- Participation in another research study involving an investigational product in the past 12 weeks or received a gene/cell-based therapy at any time previously, except if treated within an antecedent study with AAV2-REP1.

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A complete list of eligibility criteria is provided in Section 8 of the protocol (see Appendix 16.1.1).

Study Treatment, Dose, Mode of Administration:

After undergoing a standard vitrectomy and retinal detachment, participants received a subretinal injection of up to 0.1 mL of study drug containing 1×10^{11} AAV2-REP1 vg for each eye. Administration of study treatment in each eye was separated by an observational period. For participants who were treated in 1 eye in an antecedent study, only the fellow eye was treated, as described.

Duration of Treatment and Follow-Up:

This study was a 2-period, bilateral interventional safety study of AAV2-REP1. The study consisted of a Screening Period followed by 2 treatment periods (Period 1 and Period 2). The post-treatment follow-up period lasted at least 12 months per treatment period.

Criteria for Evaluation:

The following is a description of all safety and efficacy assessments that were originally planned for this study.

The timing of these assessments can be found in the Schedule of Study Procedures, Section 16 of the protocol (see Appendix 16.1.1).

Safety:

- BCVA as measured by the 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 (AF).
- Fundus photography.
- Microperimetry.
- Adverse events (AEs).
- Vector shedding.
- Immunogenicity.
- Vital signs.

Efficacy:

- BCVA as measured by the ETDRS chart.
- AF.
- SD-OCT.
- Microperimetry.

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Statistical Methods:

General Conventions:

No formal statistical testing was performed.

Continuous variables were summarized with descriptive statistics (number of participants, mean, standard deviation, median, first/third quartiles, 5th/95th percentiles, minimum/maximum). Summary statistics were to be presented by period and overall. For selected endpoints, a summary by surgery window (short, medium, and long) is also provided. Where appropriate, summary statistics are displayed by eye (SE1 and SE2) and by period.

Categorical variables, including binary variables, were summarized by counts and percentages. The 95% 2-sided confidence interval (CI) was to be calculated where appropriate, with the CI of the mean value and mean change from baseline of an assessment calculated using the t-test formula and by the Clopper-Pearson method in the case of percentages.

Study Populations Analyzed:

The All Treated Subjects analysis set consisted of all participants who completed the "Day of Surgery" visit of Period 1 (or of Period 2, for participants who received AAV2-REP1 treatment in SE1 in an antecedent study). The All Treated Subjects analysis set was the primary population for demographics, baseline characteristics, and safety and efficacy analyses.

The analysis of variables by period included all participants who received AAV2-REP1 treatment in at least 1 study eye, while the analysis by surgery window included only participants who received AAV2-REP1 treatment in both study eyes (participants that discontinued treatment or who only received AAV2-REP1 treatment in SE2 in this study were not included).

The Immunogenicity analysis set included all participants from the All Treated Subjects analysis set with a baseline sample and at least 1 post-treatment sample evaluable for immunogenicity. The Immunogenicity analysis set was used for the immunogenicity analyses.

The number of participants included in the Immunogenicity analysis set varied at each visit because only participants with a measurement at that visit were included.

Demography and Baseline Disease Characteristics:

Demographic (sex, race, ethnicity, and age) and baseline characteristics (including weight) were summarized in the All Treated Subjects analysis set and also summarized by surgery site. Baseline ocular characteristics were to be presented by eye (SE1 and SE2) and by period.

Safety:

Visual acuity (VA) was characterized by the proportion of eyes with a decrease from baseline of ≥ 5 letters, ≥ 10 letters, and ≥ 15 letters (summarized by visit, by eye, by period, and overall).

The following ophthalmic examination assessments were summarized by visit, by eye, by period and overall:

- IOP
- Morphological changes to the anterior and posterior segments of the eye (slit lamp examination and dilated ophthalmoscopy)
- Lens opacity grade

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Descriptive summary statistics were to be presented for observed value and change from baseline in continuous endpoints and the number and percentage of participants within each category and their shift from baseline for categorial endpoints.

SD-OCT, AF, and microperimetry parameters were also summarized by visit, by eye, and by period. Observed value, change from baseline, and percent change from baseline were to be presented for continuous parameters, and the observed value for the number and percentage of participants, and shift from baseline were to be presented for categorical parameters.

Fundus photography parameters (as well as shift from baseline) were summarized by visit, by eye, and by period.

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), study drug and/or study procedure-related TEAEs/SAEs, TEAEs leading to death, and TEAEs leading to study treatment discontinuation were summarized.

Immunogenicity analyses were performed on the Immunogenicity analysis set. Three immunogenicity data sets were acquired for the study: antidrug antibodies (ADAs) to the transgenic product (REP1), antiAAV2 neutralizing antibodies (NAbs; a bioassay that measures the ability of NAbs in the patient sample to inhibit viral transduction of target cells), and enzyme-linked immunospot (ELISpot). In the ELISpot assay, 3 peptide pools derived from REP1 protein (REP1 Pool 1, REP1 Pool 2, and REP1 Pool 3) and AAV2 capsid were used to test peripheral blood mononuclear cells (PBMC) collected at each visit from each participant. The results from all 4 stimuli were combined and used to evaluate the T cell response to AAV2-REP1; the 3 REP1 pools were used to evaluate the immune response to the therapeutic gene product, and the AAV2 pool was used to evaluate the immune response to the adeno-associated virus vector.

The relationship was assessed between immunogenicity and ocular inflammation-related TEAEs, VA reduced-related TEAEs, and hypersensitivity-related TEAEs.

The number and percentage of participants who experienced post-treatment ocular inflammation-related TEAEs and the number of ocular inflammation-related TEAEs were summarized by antibody status and by period. The number and percentage of participants who experienced VA reduced-related and hypersensitivity-related TEAEs, the number of VA reduced-related and hypersensitivity-related TEAEs, as well as the number and percentage of eyes with a decrease from baseline of $\geq$ 15 letters in BCVA at Month 12 were summarized; these analyses were conducted by eye, by period, and by surgery window and repeated by AE severity (mild, moderate, and severe) and by AE time to onset ($\leq$ 30 days and > 30 days post-treatment).

Efficacy:

BCVA analysis is summarized by visit, by eye, by period, and overall.

Both continuous and categorical endpoints for BCVA were summarized by the following subgroups: age ($\leq$ 50 years or > 50 years, $\leq$ 60 years or > 60 years, and $\leq$ median age or > median age), race, region, surgery site, and surgery window (short, medium, and long).

The data for SE1 Period 2 visits were also to be presented by remapping to visits after the last visit in Period 1 and calculating the change from baseline using baseline at Period 1 for the same eye (SE1). This allows for a longitudinal analysis of the treatment journey of SE1 throughout the study. As supportive sensitivity analysis, the BCVA analysis was to be conducted using the remapped visits (observed case [OC]) and the remapped visits using last observation carried forward (LOCF) imputation method (regardless of the reasons for missing data).

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For all assessments in Periods 1 and 2 of SE1, the data records were assigned to the calculated visit window as described in the Statistical Analysis Plan (SAP; Appendix 16.1.9, Statistical Analysis Plan, Version 2.0).

AF, SD-OCT, and microperimetry were assessed as described for the primary safety endpoints.

Vector shedding is summarized by categorical results and tabulated by visit, by eye, and by period.

Vital signs (blood pressure and pulse rate), observed result as well as change from baseline, were summarized by visit and by period.

Changes in the Planned Analysis:

All changes to the planned analyses for the study were implemented by an SAP amendment, as described in Appendix 16.1.9, Statistical Methods.

Results:

All summary tables can be found in Section 2.

Participant Disposition:

A total of 82 participants were screened, 66 participants received study treatment and 16 participants were screen failures; 53 participants completed the study. A total of 13 participants discontinued treatment; 4 participants discontinued because of SAEs and 1 participant because of death.

The following participant disposition listings are provided in the respective appendices:

Listing 16.2.1.1 Subject Disposition All Enrolled Subjects	Appendix 16.2.1
Listing 16.2.1.2 Visit Dates All Enrolled Subjects	
Listing 16.2.3 Reason for Screen Failure or Withdrawal from Study Prior to Study Treatment All Enrolled Subjects	Appendix 16.2.3
Listing 16.2.5 Surgery and Study Drug Administration All Treated Subjects	Appendix 16.2.5

Demographics and Baseline Disease Characteristics:

Participants were all males (per the protocol) and ranged in age from 18 to 74 years. Most participants were White (98.5%) and not Hispanic or Latino (90.9%). A total of 6 (9.1%) participants received treatment on the first eye with AAV2-REP1 in an antecedent study.

At Baseline, the ocular characteristics of the participants in this study were representative of adults with CHM and were well balanced between study eyes.

The following demographics and baseline disease characteristics listings are provided in the respective appendices:

Listing 16.2.2 Protocol Deviations All Enrolled Subjects	Appendix 16.2.2
Listing 16.2.4.1 Demographics and Baseline Characteristics All Enrolled Subjects	Appendix 16.2.4
Listing 16.2.4.2 Non-Ocular Medical History All Treated Subjects	
Listing 16.2.4.3 Ocular Medical History All Treated Subjects	
Listing 16.2.4.4 Prior and Concomitant Medications All Treated Subjects	

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Listing 16.2.4.5 Corticosteroid Treatment/Tapering All Treated Subjects	
Listing 16.2.4.6 On-Study Surgery and Procedures All Treated Subjects	
Listing 16.2.4.7 Choroideremia (CHM) Diagnosis All Enrolled Subjects	

Efficacy:

At Day 1 post-treatment, both study eyes of most participants presented a decrease from baseline in the BCVA score. The change from baseline generally remained negative until end of study for both study eyes, despite a gradual and slow return to baseline values by Month 9.

For SE1, BCVA scores generally decreased from Baseline to Day 1 post-treatment to a lesser magnitude in the short surgery window than in the other surgery windows. In contrast, for SE2, BCVA scores generally decreased post-treatment to a greater magnitude in the medium surgery window than in the other surgery windows. A reestablishment of BCVA baseline was first observed in the short and long surgery windows in SE1 (at Month 1 and Month 3 respectively), while for SE2, a reestablishment of BCVA baseline was not observed.

The longitudinal analysis of SE1 in Period 2 using the OC for remapped visits demonstrated that the BCVA score of SE1 did not return to baseline values until Month 18 and remained mostly stable thereafter until Month 21. In addition, the increase from Baseline in BCVA score between Month 9 and Month 18 was consistently higher in the short and long surgery windows than in the medium surgery window.

Sporadic improvements from Baseline in BCVA score ≥ 10 and ≥ 15 letters were observed in SE2 during Period 1 after SE1 treatment. One participant (2.9%) from the long surgery window experienced a ≥ 10-letter improvement in SE1 through Month 15 and Month 18. However, these were considered random events. A relationship to surgery window was not demonstrated because of the low number of events that met this criterion.

Subgroup analysis of continuous and categorical endpoints for BCVA are summarized as follows:

- Categorical decreases from baseline in BCVA score in both study eyes were more frequently observed in participants > 50 years of age. Conversely, most participants with a ≥ 15-letter or ≥ 10-letter increase in BCVA were ≤ 50 years of age. Although the number of participants > 60 years of age was low, categorical BCVA results were similar to those observed for participants > 50 years of age.
- BCVA score post-treatment for SE1 was consistently lower in Europe- than US-based sites. For SE2, the results were similar between regions.
- Analyses of the mean change from baseline in BCVA score and analyses of the proportions of participants with a ≥ 15-letter or ≥ 10-letter increase from baseline in BCVA by race were not possible because of the low number of non-White participants.
- Subgroup analyses did not identify any other characteristic that showed a meaningful difference in treatment effect across subgroups. The mean change from baseline in BCVA score and the proportions of participants with a ≥ 15-letter or ≥ 10-letter increase from baseline in BCVA were consistent across surgery sites.
- Changes from baseline in BCVA score were comparable between study eyes and not affected by surgery window for all subgroups analyzed.

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The percent change from baseline of the total area of preserved AF and the square root of total area of preserved AF slowly decreased post-treatment throughout the study and the trend was similar between study eyes and among surgery windows. The decrease from baseline in distance from foveal center (FC) to nearest border of preserved AF was higher for SE1 than for SE2 throughout the study. The lesion (nonpreserved area) in the study eye at Baseline was not subfoveal in relation to FC for the majority of participants. The majority of participants had no shift in relation to FC during the study.

Shifts from baseline in vitreomacular traction, macular hole, cystoid macular edema, subretinal fluid, subretinal hyper-reflective material, and pigment epithelial detachment were infrequent throughout the study. For epiretinal membrane, the shift from absent at Baseline to present was similar between study eyes throughout the study and not influenced by surgery window.

At Baseline, the majority of participants had questionable or present intraretinal hyper-reflective spots in both study eyes; by the end of the study all participants had present intraretinal hyper-reflective spots in both study eyes. Results were comparable across all surgery windows.

Changes from baseline observed in microperimetry parameters throughout the study were transient and comparable between study eyes at Month 12. Fixation stability was similar between study eyes and not affected by surgery window.

The following efficacy listings are provided:

Listing 16.2.6.1 Visual Acuity All Treated Subjects	Appendix 16.2.6
Listing 16.2.6.2 Fundus Autofluorescence All Treated Subjects	
Listing 16.2.6.3.1 Spectral Domain Optical Coherence Tomography: Part 1 All Treated Subjects	
Listing 16.2.6.3.2 Spectral Domain Optical Coherence Tomography: Part 2 All Treated Subjects	
Listing 16.2.6.4.1 Microperimetry: Celes All Treated Subjects	
Listing 16.2.6.4.2 Microperimetry: DIRC All Treated Subjects	

Safety:

Analysis of Adverse Events

A similar percentage of participants experienced a similar number of TEAEs in Period 1 (322 events experienced by 60 participants [100%]) and Period 2 (352 events experienced by 54 participants [96.4%]).

A total of 571 ocular TEAEs were experienced by 65 participants (98.5%). The number of ocular TEAEs reported and the percentage of participants reporting ocular TEAEs in both study eyes were comparable between Period 1 (273 events experienced by 57 participants [95.0%]) and Period 2 (298 events experienced by 51 participants [91.1%]).

A similar percentage of participants reported TEAEs in all surgery windows. The number of ocular TEAEs, the associated severity, the plausible relationship to study drug and/or study procedure, and the TEAE outcome were also similar in all surgery windows.

Analysis by Preferred Term

The most frequently reported ocular TEAEs by preferred term (PT) reported in ≥ 10% of all participants were

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conjunctival hemorrhage, anterior chamber cell, VA reduced, eye pain, foreign body sensation in eyes, conjunctival hyperemia, eye irritation, IOP increased, vitreal cells, vitritis, ocular discomfort, visual impairment, conjunctival edema, vision blurred, anterior chamber flare, and dry eye.

The most frequently reported nonocular TEAEs by PT reported with an incidence ≥ 10% were nasopharyngitis and headache.

Analysis by Severity

The ocular and nonocular TEAEs reported were predominantly mild or moderate in severity. The percentage of participants reporting mild or moderate TEAEs was similar in both treatment periods.

A total of 5 nonocular TEAEs classified as severe were experienced by 3 participants (4.5%), and a total of 10 ocular TEAEs classified as severe were experienced by 8 participants (12.1%). A higher percentage of participants reported a higher number of ocular TEAEs classified as severe in Period 1 (7 events experienced by 6 participants [10.0%]) than in Period 2 (3 events experienced by 2 participants [3.6%]).

The percentage of participants reporting mild or moderate TEAEs was similar in all surgery windows. No participants in the short surgery window reported severe ocular TEAEs, whereas 2 participants (10.5%) in the medium surgery window and 1 participant (8.3%) in the long surgery window reported severe ocular TEAEs.

Analysis by Relationship to Study Drug and/or Study Procedure

Most ocular TEAEs were plausibly related to study procedure (502 events experienced by 65 participants [98.5%]), whereas 46 ocular TEAEs were plausibly related to study drug (46 events experienced by 19 participants [28.8%]). A higher percentage of participants reported serious ocular TEAEs plausibly related to study procedure (23 events experienced by 15 participants [22.7%]) than study drug-related serious ocular TEAEs (12 events experienced by 7 participants [10.6%]). No nonocular serious TEAEs were plausibly related to study drug or study procedure.

A total of 25 serious TEAEs experienced by 15 participants (22.7%) were plausibly related to study drug and/or study procedure. A higher percentage of participants reported serious TEAEs in Period 1 than in Period 2; a total of 11 participants (18.3%) in Period 1 compared with 5 participants (8.9%) in Period 2 reported at least 1 serious TEAE plausibly related to study drug and/or study procedure.

Overall, the percentage of participants reporting at least 1 serious TEAE plausibly related to study drug and/or study procedure did not differ meaningfully among participants in the 3 surgery windows. Due to the low number of serious TEAEs reported, it was not possible to establish a relationship with surgery window.

Analysis of Outcome and Onset of Treatment-Emergent Adverse Events

Most TEAEs were recovered/resolved by end of study in both treatment periods, and most TEAEs did not necessitate any action.

Overall, the percentage of participants reporting TEAEs that were not recovered/not resolved and were recovered/resolved was similar in each treatment period. A total of 17 participants (28.3%) reported 30 TEAEs that were not recovered/not resolved in Period 1, whereas 17 participants (30.4%) reported 57 events that were not recovered/not resolved in Period 2. The percentage of participants reporting TEAEs with an outcome of not recovered/not resolved and recovered/resolved was similar in all surgery windows.

A total of 2 out of 103 nonocular TEAEs experienced by 2 participants (3.0%) necessitated hospitalization, 1 in each treatment period, and both participants were randomized to the medium surgery window. No ocular TEAEs led to

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hospitalization in either treatment period or in any surgery window. The most frequent action taken for both ocular TEAEs and nonocular TEAEs was "none".

In Period 1 only, ocular TEAEs were also identified as occurring < 30 days post-treatment and > 30 days post-treatment. Most participants reported ocular TEAEs that occurred ≤ 30 days post-treatment in SE1. A total of 57 participants (95.0%) reported 228 ocular TEAEs with onset ≤ 30 days post-treatment, and 17 participants (28.3%) reported 34 ocular TEAEs with onset > 30 days. Onset time of TEAEs was similar among surgery windows.

Deaths, Serious Adverse Events, and Other Significant Events

One participant (1.8%) died as a result of completed suicide in Period 2, which was not related to study drug or study procedure.

The percentage of participants reporting serious TEAEs and serious ocular TEAEs was higher in Period 1 than in Period 2. A total of 32 serious TEAEs were experienced by 19 participants (28.8%), of which 18 events were experienced by 12 participants (20.0%) in Period 1 and 14 events were experienced by 8 participants (14.3%) in Period 2. A total of 27 serious ocular TEAEs were experienced by 16 participants (24.2%), of which 17 events were experienced by 11 participants (18.3%) in Period 1 and 10 events were experienced by 6 participants (10.7%) in Period 2.

Although the percentage of participants with reported serious TEAEs was higher for the medium surgery window (31.6%) than the short or the long surgery windows (21.1% and 16.7%, respectively), the percentage of participants who reported serious ocular TEAEs was comparable among the surgery windows (15.8%, 21.1%, and 16.7% for the short, medium, and long surgery windows respectively).

The following serious ocular TEAEs were reported by PT: VA reduced (15 participants [22.7%] with a slightly higher percentage of participants reporting events in Period 1 than Period 2 [16.7% and 10.7%, respectively]), noninfective retinitis (2 participants [3%]), blindness unilateral, choroidal neovascularization, eye inflammation, macular hole, retinal degeneration, retinal detachment, tractional retinal detachment, and vitreous hemorrhage (1 participant each [1.5%]).

The following serious nonocular TEAEs were reported by PT: appendicitis, the disease caused by a new coronavirus called SARS CoV 2 (COVID-19) pneumonia, completed suicide, depression, and pulmonary embolism (1 participant each [1.5%]).

A total of 4 participants (6.1%) discontinued treatment because of serious ocular TEAEs, all occurred in SE1 during Period 1. Because of there were no serious TEAEs leading to study discontinuation, it was not possible to establish a relationship with surgery window.

Adverse Events of Interest

Custom Medical Dictionary for Regulatory Activities queries were defined that collated all PTs potentially related to ocular inflammation or all PTs potentially related to VA reduced. Ocular inflammation-related events and VA reduced-related TEAEs were classified by time from treatment to event onset to better distinguish events that may have been attributable to the surgical procedure from those that may have been related to the study drug. These events were summarized by system organ class (SOC) and PT overall and by SOC and PT and time to onset.

Events that had the following PTs were considered to be ocular inflammation related in a formal safety signal plan: anterior chamber cell, anterior chamber fibrin, anterior chamber flare, anterior chamber inflammation, aqueous fibrin, autoimmune eye disorder, birdshot chorioretinopathy, chorioretinitis, choroiditis, cystoid macular edema, endophthalmitis, eye inflammation, hypopyon, immune-mediated uveitis, macular edema, necrotizing retinitis, noninfectious endophthalmitis, noninfective chorioretinitis, noninfective retinitis, ocular vasculitis, optic neuritis,

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panophthalmitis, retinal edema, retinal vasculitis, retinitis, sympathetic ophthalmia, toxic anterior segment syndrome, uveitis, uveitis-glaucoma-hyphema syndrome, vitreal cells, and vitritis.

Events that had the following PTs were considered to be related to VA reduced in a formal safety signal plan: altered visual depth perception, amaurosis, amaurosis fugax, blindness, blindness day, blindness transient, blindness unilateral, central vision loss, Charles Bonnet syndrome, chloropsia, chromatopsia, color blindness, color blindness acquired, cyanopsia, delayed dark adaptation, delayed light adaptation, diplopia, dyschromatopsia, eccentric fixation, erythropsia, foveal degeneration, glare, halo vision, loss of visual contrast sensitivity, low luminance best-corrected VA decreased, metamorphopsia, night blindness, photopsia, sudden visual loss, tunnel vision, vision blurred, VA reduced, VA reduced transiently, visual brightness, visual field defect, visual impairment, and xanthopsia.

Ocular inflammation-related TEAEs were observed in 44 participants (66.7%). Results were similar between study eyes in each treatment period (33 participants [55.0%] in SE1 in Period 1 and 33 participants [58.9%] in SE2 in Period 2). The most frequently reported ocular inflammation-related TEAEs (reported in ≥ 10% all participants) by PT were anterior chamber cell, vitritis, and anterior chamber flare.

The percentage of participants with reported ocular inflammation-related TEAEs was comparable among surgery windows. A total of 39 events were experienced by 14 participants (73.7%), 36 events were experienced by 11 participants (57.9%), and 33 events were experienced by 9 participants (75.0%) in the short, medium, and long surgery windows, respectively.

Ocular inflammation-related TEAEs were mostly reported to have occurred ≤ 30 days post-treatment in SE1. A total of 33 participants (55.0%) reported 51 ocular inflammation-related TEAEs with onset ≤ 30 days post-treatment, and 4 participants (6.7%) reported 5 ocular inflammation-related TEAEs with onset > 30 days.

Ocular inflammation-related TEAEs in SE1 with onset ≤ 30 days post-treatment were reported in 10 participants (52.6%), 8 participants (42.1%), and 9 participants (75.0%) in the short, medium, and long surgery windows, respectively. Ocular inflammation-related TEAEs in SE1 with onset > 30 days post-treatment were reported in 5 participants (26.3%), 2 participants (10.5%), and 3 participants (25.0%) in the short, medium, and long surgery windows, respectively. Because of the low number of ocular inflammation-related TEAEs, it was not possible to establish a relationship with surgery window.

VA reduced-related TEAEs were observed in 38 participants (57.6%). Results were similar between study eyes in each treatment period (25 participants [41.7%] in SE1 in Period 1 and 22 participants [39.3%] in SE2 in Period 2). The most frequently reported VA reduced-related TEAEs (reported in ≥ 10% all participants) by PT were VA reduced, visual impairment, and vision blurred.

The percentage of participants who reported VA reduced-related TEAEs was comparable among surgery windows (57.9%, 52.6%, and 41.7% in the short, medium, and long surgery windows, respectively).

VA reduced-related TEAEs were mostly reported to have occurred ≤ 30 days post-treatment in SE1. A total of 21 participants (35.0%) reported 28 VA reduced-related TEAEs with onset ≤ 30 days post-treatment, and 9 participants (15.0%) reported 10 VA reduced-related TEAEs with onset > 30 days.

The percentage of participants reporting VA reduced-related TEAEs with onset ≤ 30 days post-treatment was similar among surgery windows (5 participants [26.3%], 6 participants [31.6%], and 3 participants [25.0%] reported TEAEs with onset ≤ 30 days post-treatment in SE1 in the short, medium, and long surgery windows, respectively). A lower percentage of participants reported VA reduced-related TEAEs with onset > 30 days post-treatment in the medium surgery window than in the short and long surgery windows (4 participants [21.1%], 1 participant [5.3%], and 4 participants [33.3%] reported TEAEs with onset > 30 days post-treatment in SE1 in the short, medium, and long

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surgery windows, respectively). Because of the low number of VA reduced-related TEAEs and despite the variation described, it was not possible to establish a clear relationship with surgery window.

Analysis of Ocular Safety

Intraocular Pressure

No meaningful changes from baseline in IOP were observed throughout the study in either study eye or between treatment periods.

Slit Lamp Examination

Slit lamp examination assessments of cornea, conjunctiva, iris, lens, and anterior segment were evaluated as normal/clinically insignificant or clinically significant. Anterior chamber hypopyon, anterior chamber cells, anterior chamber flare, and vitreous inflammation were defined as absent or present.

Despite some transient changes throughout the study, no participants had a shift in study eye from normal/clinically insignificant abnormality (CIA) at Baseline to clinically significant abnormality (CSA) or from CSA at Baseline to normal/CIA at Month 12 for cornea, conjunctiva (except for 1 participant [1.9%] in SE1 in Period 2 from CSA at Baseline to normal/CIA at Month 12), iris, or anterior segment grading.

Shifts from normal/CIA at Baseline to CSA at Month 12 in lens grading were observed in 1 participant (6.7%) in SE1 in Period 1, 2 participants (3.8%) in SE1 in Period 2, and 1 participant (1.9%) in SE2 in Period 2.

Despite some transient changes throughout the study, no participants experienced a shift from absent at Baseline to present at Month 12 or present at Baseline to absent at Month 12 for anterior chamber hypopyon and anterior chamber flare grading.

Shifts from absent at Baseline to present at Month 12 for anterior chamber cell grading were observed for 1 participant (6.7%) in SE1 in Period 1 and 1 participant (1.9%) in SE2 in Period 2. A total of 3 participants (5.7%) experienced a shift from present at Baseline to absent at Month 12 in SE1 in Period 2.

Shifts from absent at Baseline to present at Month 12 for vitreous inflammation grading were observed for 1 participant (1.9%) in SE1 in Period 2 and 1 participant (1.9%) in SE2 in Period 2.

Lens Opacity Grades

Most participants in each treatment period had no shift in category from baseline to Month 12 in either study eyes for nuclear opalescence grade, nuclear color grade, cortical cataract grade, and posterior cataract grade. Changes from baseline to Month 12 in lens opacity were similar in both study eyes in both treatment periods.

Dilated Ophthalmoscopy

Transient or minor shifts in category from baseline to Month 12 in the dilated ophthalmoscopy assessments of the vitreous, macula, and optic nerve grading were observed. There were no shifts in category from baseline to Month 12 in the dilated ophthalmoscopy assessments of the peripheral retina and choroid grading. The results were similar between study eyes and treatment periods.

Despite some transient changes throughout the study, no participants experienced a shift from absent at Baseline to present at Month 12 or present at Baseline to absent at Month 12 for retinal tear or retinal detachment grading.

Fundus Photography

No participants experienced a shift from absent at Baseline to present at Month 12 or present at Baseline to absent at

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Month 12 for retinal pigment epithelium hyperplasia, retinal vessel sheathing, optic atrophy/pallor, and optic disc swelling grading.

Shifts from absent at Baseline to present at Month 12 for retinal arteriolar narrowing grading were observed for 3 participants (20.0%) in SE1 and 2 participants (13.3%) in SE2 in Period 1 and 1 participant (2.0%) in SE1 and 3 participants (6.1%) in SE2 in Period 2. One participant (2.0%) experienced a shift from present at Baseline to absent at Month 12 in SE1 in Period 2.

Vector Shedding

Any detection of vector DNA concentration greater than the limit of detection was considered positive. The complete bioanalytical report and a memo discussing the impact of discrepancies in the demographic information in the bioanalytical report is provided in Appendix 16.1.10.

All bilateral tear samples were negative at Baseline at each treatment period. On Day 1 post-treatment, positive samples were identified in 3 participants in Period 1, and in 1 participant in Period 2, with approximately 30 additional samples below level of quantification (vector DNA concentration above the limit of detection but too low to be quantified by the qPCR assay [BLOQ]) for each period. Vector DNA concentration titers rapidly decreased in all participants at Day 3 and Day 7. For both treatment periods, bilateral tear samples were negative for vector shedding by Day 14, with an additional 1 tear sample from Period 2 at BLOQ at that timepoint. After Day 14, no positive and no BLOQ samples were observed.

Saliva was negative at Baseline in all samples at each treatment period. On Day 1 post-treatment, positive titers were observed in 1 participant from each treatment period, with an additional approximately 20% of samples from each treatment period at BLOQ. No saliva samples were positive at Day 3; however, 1 sample was positive at Day 7 in 1 participant in Period 2. BLOQ samples decreased progressively from Day 3 to Day 7, from roughly 9% to 15% on Day 3 to roughly 3% to 5% at Day 7. After Day 14 post-treatment, no BLOQ samples were observed in either period except for 1 sample at BLOQ on Month 3 post-treatment in Period 1.

Blood was vector negative throughout the study; however, BLOQ samples were identified at Day 1 post-treatment in approximately 20% to 25% of the participants. These BLOQ samples decreased to between 9% and 17% of participants by Day 7 post-treatment and roughly 3% of participants by Day 14 post-treatment. No sample was BLOQ after 1 month.

There were no positive or BLOQ samples observed in urine in any participant at any time post-treatment.

Vital Signs

Overall, treatment with AAV2-REP1 was not associated with any change from baseline over time in vital sign measurements, and values were similar to those observed at Baseline.

The following safety listings are provided:

Table 14.3.2.1 Listing of Serious Treatment-Emergent Adverse Events All Treated Subjects All Treated Subjects	Section 2.3
Table 14.3.2.2 Listing of Treatment-Emergent Adverse Events Reported by Subjects Who Discontinued Due to SAE All Treated Subjects	
Table 14.3.2.3 Listing of Treatment-Emergent Adverse Events Leading to Death All Treated Subjects	
Listing 16.2.7.1 Adverse Events All Treated Subjects	Appendix 16.2.7

Listing 16.2.8.2.1 Intraocular Pressure (IOP) All Treated Subjects	Appendix 16.2.8
Listing 16.2.8.2.2 Slit-Lamp Biomicroscopy All Treated Subjects	
Listing 16.2.8.2.3 Lens Opacity All Treated Subjects	
Listing 16.2.8.2.4 Dilated Opthalmoscopy All Treated Subjects	
Listing 16.2.8.2.5 Fundus Photography All Treated Subjects	
Listing 16.2.8.2.6 Vital Signs All Treated Subjects	
Listing 16.2.8.2.7 Vector Shedding All Treated Subjects	

Immunogenicity Assessments

Anti-REP1 Antibodies

No samples were positive for ADAs at Baseline or post-treatment. The complete bioanalytical report and a memo discussing the impact of discrepancies in the demographic information in the bioanalytical report is provided in Appendix 16.1.10.

AAV2-Neutralizing Antibodies

NAb levels at Screening and subsequent visits were reported as the reciprocal of the highest fold of dilution (titer) needed to rid the sample of neutralizing activity against an AAV2 reporter virus. Results of "< 10" were regarded as negative, and results of "> 10" were regarded as positive.

Pre-existing immunoreactivity was defined as a positive NAb assay response at Baseline. A treatment-emergent positive result was defined as follows for NAbs:

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

In Period 1, the percentage of participants who were negative at Baseline (n = 38) and positive post-treatment remained low and relatively stable (2 to 4 participants) throughout follow-up, decreasing to no participants being positive at Month 12 post-treatment. The Period 1 participants who were positive at baseline (N = 19) remained stably positive through Month 6 (12 to 18 participants), decreasing at Month 12 to 6 participants.

In Period 2, the percentage of participants who were negative at Baseline (N = 35) and positive post-treatment (1 to 5 participants) remained low and stable throughout follow-up. In Period 2, participants who were positive at baseline (N = 21) and positive post-treatment (18 to 20 participants) remained stable throughout follow-up, decreasing to 14 positive participants at Month 12.

The highest percentage of treatment-emergent positive NAb responses was observed at Day 14 post-treatment in Period 1 (7 participants [14.0%]) and Month 1 and Month 3 in Period 2 (5 participants [10.0%]).

The complete bioanalytical report and a memo discussing the impact of discrepancies in the demographic information in the bioanalytical report is provided in Appendix 16.1.10.

ELISpot Sampling

Cellular immunity mediated by T-lymphocytes against the viral vector capsid (AAV2) and against the REP1 protein was evaluated by interferon-gamma ELISpot assay of PBMCs. Cellular immunity was evaluated at Baseline and post-treatment and was reported as positive or negative by peptide pool stimulation and as spot forming units per 10^6 PBMCs. A positive response was defined as a greater than 3-fold increase in spot counts relative to the unstimulated control (cells only). Participants with missing ELISpot data at a given visit were excluded; the results are presented only on the number of valid samples at each visit.

Of the participants with valid baseline and post-treatment timepoint ELISpot samples, the highest percentage of positive ELISpot responses against overall AAV2-REP1 was observed at Month 3 in Period 1 (5 participants [33.3%])

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and Month 6 in Period 2 (5 participants [16.1%]). Baseline results were comparable for ELISpot responses against REP1; the highest percentage of positive ELISpot responses against REP1 (from negative at Baseline to positive) was observed at Month 3 in Period 1 (5 participants [33.3%]) and Month 6 in Period 2 (4 participants [12.9%]).

The complete bioanalytical report and a memo discussing the impact of discrepancies in the demographic information in the bioanalytical report is provided in Appendix 16.1.10.

Immunogenicity and Efficacy

No samples were positive for ADAs at Baseline, and no treatment-emergent ADAs were reported. Therefore, the effect of ADAs on BCVA is not known and will not be further discussed.

In Period 1, no participants experienced a decrease from baseline in BCVA score ≥ 15 letters at Month 12, independent of the results for NAbs at Baseline. In Period 2, a decrease from baseline in BCVA score ≥ 15 letters was observed at Month 12 in 4 participants with positive baseline results for NAbs, namely 1 participant (12.5%) in SE1 and 2 participants (25.0%) in SE2 in the medium surgery window and 1 participant (25.0%) in the long surgery window.

In Period 1, no participants experienced a decrease from baseline in BCVA score ≥ 15 letters at Month 12, independent of the results for ELISpot at Baseline. In Period 2, no participants with positive ELISpot results at Baseline experienced a decrease from baseline in BCVA score ≥ 15 letters at Month 12.

However, in participants in Period 2 with negative ELISpot responses against overall AAV2-REP1, a decrease from baseline in BCVA score ≥ 15 letters was observed at Month 12, namely 3 participants in the medium surgery window (1 participant [7.1%] in SE1 and 2 participants [14.3%] in SE2) and 1 participant in the long surgery window in SE2.

Overall, more participants with baseline-positive NAbs experienced a decrease from baseline in BCVA ≥ 15 letters at Month 12 in Period 2.

No meaningful pattern was observed between the baseline ELISpot status and the BCVA decrease ≥ 15 letters at Month 12 between study eyes in both treatment periods, independent of the surgery window.

Immunogenicity and Safety

No samples were positive for ADAs at Baseline, and no treatment-emergent ADAs were reported. Therefore, the effect of ADAs on AEs of interest and will not be discussed.

The percentage of participants with positive results for NAbs that were considered treatment-emergent was consistent between treatment periods and among surgery windows and remained relatively stable throughout the study. The percentage of participants with positive post-treatment ELISpot results against overall AAV2-REP1 was consistent between treatment periods and among surgery windows.

Ocular Inflammation-Related TEAEs

Immunogenicity at Baseline

The percentage of participants reporting ocular inflammation-related TEAEs was slightly higher in participants with positive results for NAbs at Baseline than in participants with negative results at Baseline (66.7% compared with 51.5%, respectively) in Period 1; the percentage of participants reporting ocular inflammation-related TEAEs was similar between these groups in Period 2 (baseline-positive and negative NAbs 55.0% and 60.0%, respectively). The percentage of participants reporting ocular inflammation-related TEAEs was similar between study eyes, independent of the results for NAbs at Baseline.

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The percentage of participants reporting ocular inflammation-related TEAEs was higher in participants with a negative overall AAV2-REP1 ELISpot result at Baseline than in participants with a positive overall AAV2-REP1 ELISpot result at Baseline in both treatment periods (64.0% compared with 20.0%, respectively, in Period 1; 63.6% compared with 16.7%, respectively, in Period 2).

No meaningful difference was observed among surgery windows for both treatment periods at Baseline.

Most ocular inflammation-related TEAEs were mild or moderate in severity, independent of the results for NAbs and/or ELISpot at Baseline in both treatment periods. One ocular inflammation-related TEAE was categorized as severe: 1 participant in Period 1 who had a negative ELISpot response treated in the medium surgery window.

Treatment-Emergent/Post-treatment Immunogenicity

The percentage of participants reporting ocular inflammation-related TEAEs was similar between study eyes in each treatment period. The percentage of participants reporting ocular inflammation-related TEAEs with no treatment-emergent positive results for NAbs during the study was higher than the percentage of participants with at least 1 treatment-emergent positive result for NAbs during the study (60.5% and 61.0% for no treatment-emergent positive results for NAbs in Period 1 and Period 2, respectively; 40.0% and 44.4% for at least 1 treatment-emergent positive result for NAbs in Period 1 and Period 2, respectively).

The percentage of participants reporting ocular inflammation-related TEAEs was 68.4% and 51.7% for participants with no treatment-emergent positive results for ELISpot in Period 1 and Period 2, respectively, and 36.4% and 70.0% for participants with at least 1 treatment-emergent positive result for ELISpot in Period 1 and Period 2, respectively. No consistent pattern of correlation was observed between the frequency of ocular inflammation-related TEAEs and the positive ELISpot results.

No meaningful difference was observed among surgery windows for both treatment periods post-treatment.

Most ocular inflammation-related TEAEs were mild or moderate in severity, independent of the treatment-emergent/post-treatment NAbs and/or ELISpot results in both treatment periods.

The time to onset of ocular inflammation-related TEAEs was mostly ≤ 30 days independent of the results for NAbs and/or ELISpot post-treatment in SE1 Period 1. Ocular inflammation-related TEAEs with onset > 30 days were only observed for 1 participant in the short surgery window and 3 participants in the long surgery window in SE1.

VA Reduced-Related TEAEs

Immunogenicity at Baseline

The percentage of participants reporting VA reduced-related TEAEs was higher in participants with positive results for NAbs at Baseline than in those with negative results at Baseline (40.0% compared with 30.3%, respectively) in Period 1. This difference was not observed during Period 2 (35.0% and 40.0% for positive and negative results for NAbs at Baseline, respectively). No meaningful difference was observed among surgery windows for both treatment periods at Baseline.

The percentage of participants reporting VA reduced-related TEAEs was higher in participants with a negative overall AAV2-REP1 ELISpot result at Baseline than in those with a positive overall AAV2-REP1 ELISpot result at Baseline in both treatment periods (40.0% compared with 20.0%, respectively, in Period 1; 39.4% compared with 16.7%, respectively, in Period 2).

Most VA reduced-related TEAEs were mild or moderate in severity independent of the results for NAbs and/or ELISpot at Baseline in both treatment periods. The following VA reduced-related TEAEs were reported as severe: 1 event was reported in Period 1 in 1 participant who had a negative result for NAbs and was treated in the medium

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surgery window; 2 events were reported in Period 2 in 2 participants who had positive results for NAbs and were treated in the medium and long surgery windows; 1 event was reported in 1 participant in Period 1 who had a negative ELISpot results and was treated in the medium surgery window; and 2 events were reported in 2 participants in Period 2 who had negative ELISpot results and were treated in the medium and long surgery windows.

Treatment-Emergent/Post-treatment Immunogenicity

The overall percentage of participants reporting VA reduced-related TEAEs was comparable between study eyes in both treatment periods. The percentage of participants reporting VA reduced-related TEAEs was lower in participants with no treatment-emergent positive results for NAbs than in those with at least 1 treatment-emergent positive result for NAbs (28.9% and 36.6% for with no treatment-emergent positive results for NAbs in Period 1 and Period 2, respectively; 50.0% and 44.4% for at least 1 treatment-emergent positive result for NAbs in Period 1 and Period 2, respectively). However, this difference may be due to the lower number of participants with at least 1 treatment-emergent positive result for NAbs.

The percentage of participants reporting VA reduced-related TEAEs was higher in Period 2 than in Period 1 and was higher in participants with no treatment-emergent positive overall AAV2-REP1 ELISpot results (18.2% with at least 1 treatment-emergent positive result and 47.4% with no treatment-emergent positive result in Period 1; 30.0% with at least 1 treatment-emergent positive result and 37.9% with no treatment-emergent positive result in Period 2).

No meaningful difference was observed among surgery windows for both treatment periods post-treatment, independent of any treatment-emergent positive results for NAbs or ELISpot during the study.

Most VA reduced-related TEAEs were mild or moderate in severity independent of the results for NAbs post-treatment in both treatment periods. The following VA reduced-related TEAEs were reported as severe: 1 event in 1 participant in Period 1 who had a negative result for NAbs post-treatment and who was treated in the medium surgery window; 2 events in 2 participants who had negative results for NAbs post-treatment and who were treated in the medium and long surgery windows, respectively, in Period 2; 1 event in 1 participant in Period 1 who had a negative overall AAV2-REP1 ELISpot result post-treatment and who was treated in the medium surgery window; and 2 events in 2 participants who had negative overall AAV2-REP1 ELISpot results post-treatment and were treated in the medium and long surgery windows, respectively, in Period 2.

The time to onset of VA reduced-related TEAEs was mostly ≤ 30 days in SE1 and independent of the results for NAbs and/or ELISpot post-treatment (24.2% and 40.0% for negative and positive for NAbs at Baseline, respectively; 32.0% and 20.0% for negative and positive for overall BIB111 ELISpot at Baseline, respectively). VA reduced-related TEAEs with onset > 30 days were experienced by 9.1% of the participants with negative results for NAbs at Baseline and 13.3% of participants with positive results for NAbs at Baseline.

Hypersensitivity-Related TEAEs

Immunogenicity at Baseline

Hypersensitivity-related TEAEs are defined in Appendix 16.1.10.

The percentage of participants reporting hypersensitivity-related TEAEs was similar between study eyes in each treatment period, independent of the baseline results for NAbs or ELISpot. No meaningful trend or pattern was observed among surgery windows for both treatment periods at Baseline.

All hypersensitivity-related TEAEs were mild in severity independent of the results for NAbs or ELISpot at Baseline in both treatment periods.

Treatment-Emergent/Post-treatment Immunogenicity

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The percentage of participants reporting hypersensitivity-related TEAEs was similar for participants with no treatment-emergent positive results for NAbs (23.7%) and those with at least 1 treatment-emergent positive result for NAbs (20.0%) in Period 1. Similar results were observed for Period 2 (12.2% for no treatment-emergent positive result for NAbs compared with 11.1% for at least 1 positive treatment-emergent result for NAbs in SE2 in Period 2).

The percentage of participants reporting hypersensitivity-related TEAEs was higher in participants with no treatment-emergent positive ELISpot results than in those with at least 1 treatment-emergent positive ELISpot result (15.8% and 9.1%, respectively, in Period 1; 17.2% and 0% respectively in Period 2).

The percentage of participants reporting hypersensitivity-related TEAEs was comparable among surgery windows in both treatment periods post-treatment, independent of any treatment-emergent positive results for NAbs or ELISpot during the study.

All hypersensitivity-related TEAEs were mild in severity, and most hypersensitivity-related TEAEs were reported to have occurred ≤ 30 days post-treatment in SE1, independent of the results for NAbs or ELISpot post-treatment in both treatment periods.

The following immunogenicity listings are provided:

Listing 16.2.8.1.1 Immunogenicity – Neutralizing Timrepigene Emparvovec Antibodies (NAbs) Immunogenicity Analysis Set	Appendix 16.2.8
Listing 16.2.8.1.2 Immunogenicity – Anti-Drug-Antibodies (ADA) Immunogenicity Analysis Set	
Listing 16.2.8.1.3 Immunogenicity – ELISpot Immunogenicity Analysis Set	
Listing 16.2.8.1.4 Immunogenicity – Adverse Events of Interest by Immunogenicity Analyte Status Immunogenicity Analysis Set	

Conclusions:

The study did not demonstrate the efficacy of a bilateral single dose of AAV2-REP1 in each eye in participants with CHM:

- The proportion of participants with ≥ 10- and ≥ 15-letter improvement in BCVA from baseline was low. An improvement from baseline in BCVA score was not observed post-treatment in SE1 or SE2.
- Age may have been a risk factor for a poor outcome since the decrease from baseline in BCVA score was greater in participants > 50 years of age compared to participants ≤ 50 years of age.
- Region-specific differences were potentially random since the response in SE1 was different from the response in SE2.
- Changes from baseline in AF, SD-OCT, and microperimetry parameters were not meaningful throughout the study for either study eye, suggesting that outcomes are not influenced by prior exposure to AAV2-REP1 and further supporting the lack of BCVA improvement.
- The various analyses of BCVA, both categorical and continuous, suggest that prior exposure to AAV2-REP1 does not affect BCVA outcomes.
- An expected decrease from baseline in BCVA score was observed in the immediate 30 days post-treatment; this finding was considered appropriate to a normal post-treatment recovery.
- Despite some minor transitional changes in participant response, the efficacy results were also comparable independent of the surgery window.

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The safety profile of a bilateral single dose of AAV2-REP1 in each eye was determined to be acceptable and comparable independent of the surgery window or treatment order:

- The number of events and the percentage of participants reporting any TEAEs, ocular TEAEs, and nonocular TEAEs were similar between study eyes in each treatment period. The number of TEAEs, the severity of events, the plausible relationship to study drug and/or study procedure, and the TEAE outcome were similar in all surgery windows.
- The TEAEs reported were predominantly mild or moderate in severity. The majority of the reported TEAEs did not necessitate hospitalization or additional procedures and were recovered/resolved by end of study.
- Most TEAEs reported in SE1 occurred ≤ 30 days post-treatment. These results suggest that the TEAEs reported in SE1 were the expected response to surgery and that responses due to an inflammatory response to treatment in SE1 were rare. Because AE onset was calculated as the day of onset minus the day of the first surgery in the study, this definition limited the ability to make conclusions for SE2.
- A higher percentage of participants reported serious TEAEs or serious ocular TEAEs in Period 1 than in Period 2, suggesting that prior exposure to AAV2-REP1 does not increase the risk or occurrence of serious TEAEs or serious ocular TEAEs in the fellow eye (SE2). Proportionally, more participants in the medium surgery window reported serious TEAEs than in the short or long surgery windows, but the difference among surgery windows narrowed when serious ocular TEAEs were compared.
- Similarly, a higher percentage of participants reported severe ocular TEAEs in Period 1 than in Period 2. This observation parallels the results of serious TEAEs and serious ocular TEAEs, i.e., that prior AAV2-REP1 exposure does not appear to have negatively impacted the number of participants who developed severe ocular TEAEs subsequent to second eye treatment.
- No meaningful conclusion can be drawn by comparing the occurrence of severe ocular TEAEs across different surgery windows because of the small sample size.
- Administration of AAV2-REP1 was associated with ocular inflammation-related TEAEs for approximately two-thirds of the participants, and reduced VA reduced-related TEAEs for approximately half of the participants. Results were similar between study eyes in each period, independent of surgery window.
- No meaningful changes from baseline in ophthalmic examination assessments, SD-OCT, AF, fundus photography, or microperimetry were observed throughout the study in either study eye or between treatment periods.
- No samples were positive for ADAs at Baseline, and no treatment-emergent ADAs were reported. Therefore, there were insufficient data to evaluate the effect of a positive ADA result at Baseline or positive treatment-emergent ADAs on BCVA or AEs of interest.
- Approximately one third of the participants were baseline-positive for NAbs. This is consistent with the published seroprevalence of NAbs ranging from 30% to 60% in the population [Verdera 2020].
- The majority of participants with available immunogenicity data had a negative ELISpot response at Baseline. A low number of participants developed treatment-emergent or post-treatment positive ELISpot responses.

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- A pre-existing result for NAbs and/or ELISpot at Baseline or treatment-emergent/post-treatment positive response for NAbs and/or ELISpot did not appear to be associated with higher percentage of participants reporting hypersensitivity-related TEAEs.
- A pre-existing result for NAbs at Baseline appeared to be associated with a higher percentage of AAV2-REP1-treated participants reporting ocular inflammation- or VA reduced-related TEAEs in study eyes during Period 1.
- Participants with at least 1 treatment-emergent positive result for NAbs during the study reported a higher number of VA reduced-related TEAEs in the study eyes in Period 1, more pronounced than in the study eyes in Period 2. The significance of this finding is not entirely clear, as the NAb positive status in the peripheral blood (baseline or treatment-emergent) may not accurately reflect the local immunological milieu in the treated eye. Similar results were not observed for ocular inflammation-related TEAEs.
- A positive immunogenicity assay result for ELISpot at Baseline or treatment-emergent/post-treatment did not appear to be associated with a higher percentage of participants reporting ocular inflammation-related or VA reduced-related TEAEs.
- A pre-existing positive result for ELISpot at Baseline did not appear to be associated with a higher percentage of participants reporting BCVA decrease ≥ 15 letters from baseline at Month 12. Conversely, a pre-existing positive result for NAbs at Baseline appeared to be associated with a higher proportion of participants reporting BCVA decrease ≥ 15 letters from baseline at Month 12.
- No meaningful trend or pattern was observed among the 3 surgery windows in reviewing the immunogenicity data by baseline or treatment-emergent ADA, NAb, or ELISpot, suggesting that the interval of time between treatment of the first and second eye did not affect the outcome. However, because of the small sample size and sample availability, the conclusions of the comparison among the surgery windows are limited.
- Administration of corticosteroids is broadly used as a measure to limit the ocular inflammation-related TEAEs derived from the administration procedure and to modulate vector immunogenicity, as in the current study. A more effective immunomodulatory regimen would be warranted to decrease vector immunogenicity in ocular gene therapy.

Date of Report: 04 May 2023

Version: 1

2. TABLES REFERENCED, BUT NOT INCLUDED IN THE TEXT

2.1. Study Participants

NSR-REP-02 Study Participants Tables

2.2. Efficacy Data

NSR-REP-02 Efficacy Tables

2.3. Safety Data

2.3.1. Narratives of Deaths, Serious Adverse Events, and Other Significant Adverse Events

Narratives for deaths, SAEs, and AEs that resulted in discontinuation of study treatment or withdrawal from the study are presented in Appendix 16.2.7.

2.3.2. Summary of Adverse Events

NSR-REP-02 Summary of Adverse Events Tables

2.3.3. Summary of Immunogenicity

NSR-REP-02 Summary of Immunogenicity Tables

2.4. Additional Information on Study Design and Implementation

Table 1: Vendors That Participated in Study NSR-REP-02 (273CH203)

Vendor Name	Vendor Address	Responsibilities
[redacted]	[redacted] UK	Monitoring, project management, biostatistics, Ethics Committee/Institutional Review Boards submissions
[redacted]	[redacted] USA	Central laboratory vendor in scope for the collection and reconciliation of site shipments for laboratory analysis at the [redacted] site
[redacted]	[redacted] UK	PBMC immunoassay (ELISpot) analysis
[redacted]	[redacted] USA	Serum ADA analysis

Vendor Name	Vendor Address	Responsibilities
[redacted]	[redacted] UK	Vector shedding analysis
[redacted]	[redacted] USA	PBMC (ELISpot) processing for French site
[redacted]	[redacted] USA	PBMC (ELISpot) processing for US sites
[redacted]	[redacted] France	Serum NAb analysis
[redacted]	[redacted] USA	Handling, storage, and grading of ophthalmic images
[redacted]	[redacted] USA	Safety case processing
[redacted]	[redacted] USA	Safety case processing
[redacted]	[redacted] Philippines	Safety reporting for France
[redacted]	[redacted] USA	Global safety database
[redacted]	[redacted] USA	Provision of database design, data management, SDTM creation, statistical analysis, biostatistical and programming services
[redacted]	[redacted] USA	Data management
[redacted]	[redacted] Germany	Provider of CIRRUS Electronic Data Capture
[redacted]	[redacted] UK	Management of participant expenses
[redacted]	[redacted] UK	Digital file management
[redacted]	[redacted] USA	Safety translations

Vendor Name	Vendor Address	Responsibilities
[redacted]	[redacted] USA	Translation vendor
[redacted]	[redacted] UK	Printing services
[redacted]	[redacted] USA	Equipment rental and ancillary items to sites

3. REFERENCES

Verdera HC, Kuranda K, Mingozzi F. AAV Vector Immunogenicity in Humans: A Long Journey to Successful Gene Transfer. Mol Ther. 2020;28(3):723-746. Epub 2020/01/10.