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)
NCT Number:	NCT03496012
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Name of Sponsor/Company:	Biogen
Name of Finish Product:	AAV2-REP1 (timrepigene emparvovec)
Name of Active Ingredient:	AAV2-REP1
Study Indication:	Choroideremia

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The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2. STUDY SYNOPSIS

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Title of Study:

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Principal Investigator/Coordinating Investigator:

[redacted], MB ChB DPhil [redacted] United Kingdom)

Study Period: Study Start Date: 11 December 2017 End of Study Date: 01 December 2020	**Phase of Development:** 3

Study Objectives:

The objective of the study was to evaluate the efficacy and safety of a single subretinal injection of timrepigene emparvovec in participants with choroideremia (CHM).

Study Design:

This was a Phase 3, outcomes-assessor masked, prospective, randomized, parallel-controlled group, multicenter, global, interventional study of timrepigene emparvovec in male participants with genetically confirmed CHM.

The study consisted of 8 visits with a 12-month evaluation period. During the Screening/Baseline period, each participant was assessed for eligibility. For eligible participants, a study eye was assigned and the participants were randomized in a 2:1:2 ratio to receive either timrepigene emparvovec high-dose (1.0×10^{11} vector genomes [vg]) or timrepigene emparvovec low-dose (1.0×10^{10} vg) or to enter the untreated control group.

On the Injection Day Visit (Visit 2, Day 0), participants in the timrepigene emparvovec high- and low-dose treatment arms underwent vitrectomy and retinal detachment and received a subretinal injection of the assigned treatment dose of timrepigene emparvovec in their study eye; these participants then returned to the surgical site for 2 postoperative follow-up visits on Day 1 (Visit 3) and Day 7 (Visit 4). Participants in the control group did not undergo surgery, receive any study drug in their study eye (i.e., control study eye), or attend clinic on Day 0 or the

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2 postoperative visits. Instead, a telephone contact from the site occurred for the control group on Day 0 (Visit 2), Day 1 (Visit 3) and Day 7 (± 3 days; Visit 4).

Day 0 (Visit 2) was defined as the projected surgery day for participants randomized to the control group and the actual surgery day for participants randomized to the treated groups.

All participants were followed for 12 months from Visit 2 (Day 0).

Study data were collected for both eyes of each participant. Since timrepigene emparvovec treatment requires an invasive surgical procedure under general anesthesia, the sponsor, investigator, and the participant were unmasked to the study procedure (i.e., vitrectomy and subretinal injection). However, within the treated groups, the sponsor, investigator, and participant were 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) onward (including the Month 12 Primary Endpoint evaluation) were conducted by a masked assessor.

Participants were assessed for efficacy and safety throughout the study. Participants who developed cataracts may have undergone cataract surgery if deemed clinically necessary; if surgery was performed, it was carried out at least 4 weeks before the Month 12 Visit/End-of-Study Visit.

Number of Participants (Planned and Analyzed):

Planned: Approximately 160 participants were expected to be enrolled.

Analyzed: A total of 169 participants (timrepigene emparvovec high-dose group, n = 69; timrepigene emparvovec low-dose group, n = 34; control group, n = 66) were randomized; 164 participants (high-dose group, n = 65; low-dose group, n = 34; control group, n = 65) completed surgery (timrepigene emparvovec groups) or attended a postbaseline study visit (control group) and comprised the Safety Population.

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Study Population:

Main Inclusion Criteria

- Male and ≥ 18 years of age
- Documented genetically confirmed diagnosis of CHM
- Active disease clinically visible within the macular region in the study eye
- Best-corrected visual acuity (BCVA) of 34 to 73 ETDRS (Early Treatment of Diabetic Retinopathy Study) letters (equivalent to worse than or equal to 6/12 or 20/40 Snellen acuity, but better than or equal to 6/60 or 20/200 Snellen acuity) in the study eye)

Exclusion Criteria:

Participants were not eligible for study participation if they met any of the following exclusion criteria:

- Had a history of amblyopia in the eligible eye
- Were unwilling to use barrier contraception methods, or abstain from sexual intercourse, for a period of 3 months following treatment with timrepigene emparvovec
- Had previous intraocular surgery performed in the study eye within 3 months of Visit 1
- Had any other significant ocular or non-ocular disease/disorder which, in the opinion of the Investigator, may have put the participants at risk because of participation in the study, may have influenced the results of the study, or may have impacted the participant's ability to participate in the study. This included, but was not limited to, the following:
  - contraindication to oral corticosteroid
  - clinically significant cataract
  - unsuitability for subretinal surgery
- Had participated in another research study involving an investigational product in the past 12 weeks or received a gene/cell-based therapy at any time previously.

Study Treatment, Dose, Mode of Administration:

Up to 100 µL timrepigene emparvovec (1.0×10^{11} vg [high-dose] or 1.0×10^{10} vg [low-dose]) as a single subretinal injection.

Comparator Therapy/Therapies, Dose, Mode of Administration:

No control study medication/procedure was used. Participants having surgery and administered timrepigene emparvovec were compared with the untreated control group. The untreated fellow eye was also used as a comparator in supportive analysis.

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Duration of Treatment and Follow-Up:

- Screening period: Up to 8 weeks
- Treatment: A single subretinal injection was administered on Day 0
- Post-treatment period: Up to 12 months

Criteria for Evaluation:

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

Efficacy:

Primary Efficacy Endpoint:

- The proportion of participants with a ≥ 15-letter improvement from baseline in BCVA at Month 12 as measured by the ETDRS chart

Key Secondary Endpoints:

- Change from baseline in BCVA at Month 12 measured by the ETDRS chart
- Proportion of participants with a ≥ 10-letter improvement from baseline in BCVA at Month 12 measured by the ETDRS chart
- Proportion of participants 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

[redacted]

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Safety:

- Overall AEs, SAEs, and AEs/SAEs leading to discontinuations
- Clinical laboratory assessments
- IOP
- SLE
- Lens opacity
- Dilated fundoscopy
- Fundus photography
- Immunogenicity

Statistical Methods:

Demographics and Baseline Disease Characteristics: Demographics (sex, race, ethnicity, age, age group, and baseline weight) were summarized for the Safety and Intent-to-Treat (ITT) populations by treatment group and overall. Sex, race, age group, and ethnicity were summarized using summary statistics for categorical variables. Age and baseline weight were summarized using summary statistics for continuous variables.

Medical History: Medical history was coded using the Medical Dictionary for Regulatory Activities Version 23.1. The number and percentage of subjects under each history term, coded by system organ class and preferred term, were summarized by treatment. All percentages were based on the number of participants in the Safety Population within each treatment group.

Ocular History: Ocular history was summarized by treatment and eye, by system organ class and preferred term, for the Safety Population.

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Efficacy – Primary Endpoint: The primary endpoint was the proportion of participants with a ≥ 15-letter increase from baseline in BCVA at the Month 12 Visit (primary endpoint of the participant was imputed as a failure if the participant had a BCVA value missing at Month 12 as the primary analysis).

The primary endpoint was compared between study arms (high-dose vs. control, low-dose vs. control) using the Fisher's Exact test. The primary approach was the unstratified analysis, and a supportive analysis was conducted with the Cochran-Mantel-Haenszel approach by stratifying by surgical group; a supportive analysis was conducted using Fisher's Exact-Boschloo test with a Berger-Boos correction of beta = 0.001. To maintain the test at 0.05 two-sided level, the reported p-value was 2 times the one-sided p-value from the Fisher's Exact-Boschloo test. Sensitivity analysis was conducted using Last Observation Carried Forward (LOCF) to assess the impact of missing data.

The primary analysis of the primary endpoint was based on the ITT Population and a supportive analysis was performed based on the Per-Protocol (PP) and Randomized Populations. Additional supportive analyses were conducted by comparing the study eyes versus the fellow eyes (i.e., contralateral control) within the low-dose and the high-dose treatment group using the paired McNemar test.

Efficacy – Key Secondary Endpoints:

The binary efficacy endpoints were analyzed with the same methods (primary analysis, supportive analyses, and sensitivity analysis) used for the primary efficacy endpoint with missing values imputed as failures as the primary analysis. Sensitivity analysis was conducted using LOCF to assess the impact of missing data.

The continuous efficacy endpoint was analyzed by analysis of covariance (ANCOVA) including surgical group, baseline value of the assessment, and study arms. Missing data were handled by the LOCF approach.

Additional supportive analysis was conducted by comparing the study eyes versus the fellow eyes (i.e., contralateral control) within the low-dose and the high-dose treatment groups. The continuous efficacy endpoints were analyzed using the linear mixed model where the 2 eyes are considered correlated within each participant. The model included the variables of baseline assessment, treatment group, surgical group, eye and the treatment*eye interaction, where eye variable acts as the repeat variable.

The primary analysis of the key secondary endpoints was based on the ITT Population, and supportive analyses were performed based on the Randomized Population and the PP Population.

Safety: With the exception of analyses of immunogenicity data, safety analyses were performed using the Safety Analysis Set.

Immunogenicity: Immunogenicity data analysis will be presented as an addendum to the completed CSR.

Results:

Participant Accountability:

169 participants (timrepigene emparvovec high-dose group, n = 69; timrepigene emparvovec low-dose group, n = 34; control group, n = 66) were randomized; 164 participants (high-dose group, n = 65; low-dose group, n = 34; control group, n = 65) completed surgery (timrepigene emparvovec groups) or attended a postbaseline study visit (control group) and comprised the Safety Population. Four participants randomized to the high-dose group discontinued from the study before surgery and 1 participant randomized to the control group discontinued from the study before the first postrandomization study visit. Three additional participants in the control group discontinued from the study postrandomization.

Demographics and Baseline Disease Characteristics:

- Demographics in the Safety Population were generally balanced across the 3 study groups. Participants were all males (per protocol) and ranged in age from 18 to 79 years (mean [SD]: 48.7 [13.15] years). Most participants were White (87.8%) and not Hispanic or Latino (79.9%).
- At Baseline, the ocular characteristics of the study eye of participants in this study were representative of adult patients with CHM and were well balanced between study eyes.
- The study eye was similarly distributed between OS (51.6%) and OD (48.4%). Mean (SD) BCVA scores in the study eye were 58.7 (8.86), 61.8 (8.10) and 60.4 (8.66) letters for the high-dose, low-dose, and control groups, respectively. Baseline imaging parameters such as [redacted], central ellipsoid area, and MP mean sensitivity were well balanced across the cohorts and were consistent with that anticipated in this population.

Efficacy:

The study did not meet its primary efficacy endpoint. The difference between the proportion of participants in the high-dose group (n = 3 [4.6%]) and control group (n = 0 [0.0%]) experiencing a ≥ 15-letter improvement from baseline in BCVA at Month 12 in the ITT Population was not statistically significant (p = 0.245 [Fisher's Exact test]).

Analyses of the 3 key secondary efficacy endpoints were performed under a hierarchical procedure in order to maintain the type I error for the comparison between the high-dose group and the untreated control group. Although the primary endpoint was not met, these key secondary endpoints were subsequently explored through statistical analyses to more fully understand the efficacy signals associated with timrepigene emparvovec. These analyses were not used to define study success (i.e., statistical significance could not be claimed for any of the 3 key secondary efficacy endpoints).

The first key secondary endpoint was the change from baseline in BCVA score at Month 12 between the high-dose group and the control group). Based on ANCOVA (ITT Population), the least squares mean difference in the change from baseline in the study eye BCVA score at Month 12 between the high-dose group and the control group (2.1 ETDRS letters) was not statistically significant (p = 0.317).

Although the second key secondary endpoint (comparison of proportion of participants with a ≥ 10-letter improvement from baseline in BCVA at Month 12 between the high-dose group and the control group) had a p-value of 0.017, which is less than the prespecified threshold of 0.05, statistical significance could not be claimed per the hierarchical testing procedure. A greater proportion of participants in the high-dose group (n = 9 [13.8%]) in the ITT Population experienced a ≥ 10 letter improvement from baseline in BCVA in the study eye at Month 12 compared with the control group (n = 1 [1.6%]).

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The third key secondary endpoint [comparison of proportion of participants with no decrease from baseline in BCVA or a decrease of < 5 ETDRS letters from baseline in BCVA in the study eye at Month 12 between the high-dose group (n = 54 [83.1%]) and the control group (n = 42 [67.7%])] was not statistically significant (p = 0.062). The difference between the proportion of participants in the low-dose group (n = 24 [70.6%]) and control group (n = 42 [67.7%]) experiencing no decrease from baseline in BCVA or a decrease of < 5 ETDRS letters from baseline in BCVA in the study eye at Month 12 was not statistically significant (p = 0.822).

Some imaging-based measures of efficacy worsened rather than improved in the study eyes of treated participants; this may have been due to the surgical procedure causing damage to the already compromised retinal structures.

Safety:

The safety profile of timrepigene emparvovec was determined to be acceptable. No participants died during the study and none of the participants withdrew from the study due to treatment-emergent adverse events (TEAEs).

Most TEAEs were mild or moderate in severity.

A higher percentage of participants in the timrepigene emparvovec treatment groups had ocular TEAEs or ocular serious adverse events (SAEs) in the study eye compared with the control group.

Most TEAEs in the timrepigene emparvovec treatment groups were related to the study procedure rather than to the study drug.

Ocular inflammation-related TEAEs and visual acuity reduced-related TEAEs were common and occurred more frequently in the timrepigene emparvovec treatment groups. The majority of ocular inflammation-related TEAEs occurred within 30 days of study drug administration/surgery and were likely related to the surgical procedure.

The occurrence of ocular inflammation-related and visual acuity reduced-related events were not dose dependent.

Conclusions:
The study did not demonstrate efficacy of timrepigene emparvovec in improving BCVA of participants with CHM. The safety profile of timrepigene emparvovec was determined to be acceptable.

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