Clinical trial results:
An open label Phase 2 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)

Summary

EudraCT number	2015-001383-18
Trial protocol	GB
Global end of trial date	23 July 2021

Results information

Result version number	v1 (current)
This version publication date	28 October 2022
First version publication date	28 October 2022
Summary attachment (see zip file)	BCVA ETDRS Scores, Full Dataset (BCVA ETDRS Scores, Full Dataset.pdf) BCVA ETDRS Score Change from Baseline (BCVA ETDRS Score Change from Baseline.pdf) BCVA ETDRS Score Change from Baseline, Between Eye Comparison (BCVA ETDRS Score Change from Baseline, Between Eye Comparison.pdf) BCVA ETDRS Score Change from Baseline by Surgery site (BCVA ETDRS Score Change from Baseline by Surgery site.pdf)

Trial information

Trial identification

Sponsor protocol code	REGENERATE (PID 11351)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02407678
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Boundary Brook House, Churchill Drive, Oxford, United Kingdom, OX3 7LQ
Public contact	Research Governance, Ethics & Assurance Team, Research Services, ctrg@admin.ox.ac.uk
Scientific contact	Ophthalmology Trials Unit, Nuffield Laboratory of Ophthalmology, trials@eye.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2021
Global end of trial reached?	Yes
Global end of trial date	23 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigation of the efficacy and safety of a single subretinal injection of a recombinant adeno-associated virus serotype 2 (AAV2) vector encoding Rab-escort protein 1 (REP1), designated as AAV2-REP1, in subjects with a confirmed diagnosis of choroideremia over a 2-year assessment period following treatment.

Efficacy was primarily quantified by tracking the comparative change from baseline in best corrected visual acuity (BCVA) in the treated eye and untreated contralateral eye (control eye), measured by the number of letters read on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

Protection of trial subjects:

The method of vector administration was refined in an antecedent Phase 1/2 interventional study (EudraCT 2009-014617-27) where initial detachment of the retina was effected as a first step by injecting a small volume of balanced salt solution underneath the retina through a very fine needle that is narrower than a human hair, thereby creating a small fluid-filled blister or bleb under the retina. This was followed by injection of an exact dose of the adeno-associated viral (AAV) vector suspension into the subretinal fluid as a second step. The small area of retinal detachment is temporary and disappears over about 24 hours as the fluid gets slowly absorbed by the retina. This type of surgery normally lasts about an hour, and the operation itself (without administration of the gene therapy) is a routine procedure for patients with conditions such as retinal detachment.

The benefit of the preceding two-step procedure is that the slightly unpredictable part of the procedure (the retinal detachment) is completed before any AAV vector is administered to the subject. This allows for the management of any surgical complications without concerns about AAV vector dissemination.

An additional safety feature introduced in this Phase 2 interventional study was the use of an ophthalmic operating microscope with an integrated optical coherence tomography (OCT) scanner for conducting the retinal surgery. This special operating microscope shows a cross section of the retina in real time to the surgeon, thereby permitting administration of the gene therapy to be conducted far more precisely, safely and reliably.

Background therapy:

In order to minimise postoperative inflammation, subjects were given a 45 day course of oral prednisolone, starting 3 days before surgery at a daily dose of 1 mg per kg of body weight (rounded to the nearest multiple of 5 mg), and gradually tapering off to 5 mg over the course of the next 42 days.

Evidence for comparator:

Not applicable: no comparator was used in the study.

Actual start date of recruitment	16 August 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 30 subjects were recruited over the period 2016-2019, comprising 12 subjects recruited and treated at Oxford Eye Hospital and 18 subjects recruited and treated at Moorfields Eye Hospital (London).

Pre-assignment

Screening details:

Subjects were males aged 18 years or older with:
• A clinical diagnosis of choroideremia and a molecular diagnosis of a null mutation in the gene encoding REP1.
• Active disease visible clinically within the macula region.
• BCVA better than or equal to 6/60 (20/200) in the eye to be treated.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open label study with no masking. However, in order to minimise bias evaluation of the treated eye and untreated contralateral eye (control eye), ophthalmic assessments were conducted by an appropriately qualified masked observer once the subjects' treated eyes had regained their normal appearance and function following the surgical procedure.

Arms

Are arms mutually exclusive?	No
Arm title	Cohort 1

Arm description:

Cohort 1 comprised all subjects that participated in the study, and compared changes in BCVA and other measures of visual function in the treated eye against baseline values.

Arm type	Experimental
Investigational medicinal product name	AAV2-REP1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

AAV2-REP1 vector suspension (10e12 vector particles per mL) was supplied by Nightstar Therapeutics. Up to 0.1 mL of AAV2-REP1 vector suspension, corresponding to a dose of up to 10e11 vector particles, was administered to the treated eye by subretinal injection.

Arm title	Cohort 2

Arm description:

Cohort 2 comprised the subset of subjects having symmetrical disease for whom selection of the treated eye was randomized, and compared changes in BCVA and other measures of visual function in the treated eye and the untreated contralateral (control) eye. Note that randomization was not used for assigning treatment (versus placebo/standard care as in randomized controlled trials), but solely for selection of the eye to be treated in these subjects for whom the progress of retinal degeneration was relatively symmetrical for both eyes, defined as a difference in BCVA of no more than one line of letters measured on an ETDRS chart, and no more than 25% difference in the area of surviving retinal pigment epithelium measured by fundus autofluorescence.

Arm type	Experimental

Investigational medicinal product name	AAV2-REP1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

AAV2-REP1 vector suspension (10e12 vector particles per mL) was supplied by Nightstar Therapeutics. Up to 0.1 mL of AAV2-REP1 vector suspension, corresponding to a dose of up to 10e11 vector particles, was administered to the treated eye by subretinal injection.

Number of subjects in period 1	Cohort 1	Cohort 2
Started	30	28
Completed	30	28

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	30	30	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	30	30	

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Cohort 1 comprised all subjects that participated in the study, and compared changes in BCVA and other measures of visual function in the treated eye against baseline values.

Reporting group title	Cohort 2

Reporting group description:

Cohort 2 comprised the subset of subjects having symmetrical disease for whom selection of the treated eye was randomized, and compared changes in BCVA and other measures of visual function in the treated eye and the untreated contralateral (control) eye. Note that randomization was not used for assigning treatment (versus placebo/standard care as in randomized controlled trials), but solely for selection of the eye to be treated in these subjects for whom the progress of retinal degeneration was relatively symmetrical for both eyes, defined as a difference in BCVA of no more than one line of letters measured on an ETDRS chart, and no more than 25% difference in the area of surviving retinal pigment epithelium measured by fundus autofluorescence.

Primary: BCVA change from baseline in treated eye

End point title	BCVA change from baseline in treated eye[1]

End point description:

Change from baseline in BCVA (measured as change in ETDRS letters) in the treated eye. [Statistical analysis: 95% Confidence Interval of the mean change based on t-test.]

End point type	Primary

End point timeframe:

The 24-month assessment period following treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis is provided in the attached PDF file "BCVA ETDRS Score Change from Baseline", with additional information provided in the attached PDF file "BCVA ETDRS Score Change from Baseline by Surgery site".

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: ETDRS letters				
arithmetic mean (confidence interval 95%)	-2.6 (-8.3 to 3.0)	-3.2 (-9.2 to 2.8)		

Statistical analyses

No statistical analyses for this end point

Primary: BCVA change from baseline in treated eye compared with control eye

End point title	BCVA change from baseline in treated eye compared with control eye[2][3]

End point description:

Change from baseline in BCVA (measured as change in ETDRS letters) in the treated eye compared with the control eye. [Statistical analysis: 95% Confidence Intervals of the least squares mean difference

from the untreated eye. The ANCOVA (analysis of covariance) model includes the least squares mean difference in BCVA (treated eye versus control eye) as a factor and baseline BCVA as a covariate (p-value 0.059).]

End point type	Primary

End point timeframe:

The 24-month assessment period following treatment.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis is provided in the attached PDF file "BCVA ETDRS Score Change from Baseline, Between Eye Comparison".
[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis is provided in the attached PDF file "BCVA ETDRS Score Change from Baseline, Between Eye Comparison".

End point values	Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: ETDRS letters				
least squares mean (confidence interval 95%)	-5.9 (-12 to 0.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety[4]

End point description:

Serious Adverse Events (SAEs) related to the study drug (AAV2-REP1 vector) and/or the surgical procedure (vitrectomy, retinal detachment and subretinal injection of the vector suspension).

End point type	Secondary

End point timeframe:

The 24-month assessment period following treatment.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Serious adverse events are detailed in the "Adverse events" section of the report.

End point values	Cohort 1			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: SAEs related to the study drug/procedure	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The recording and follow-up of all adverse events was carried out until the end of the study, corresponding to the date of the last subject's final follow-up visit at the end of the 2-year assessment period following treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Cholelithotomy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Investigations			
Inflammatory marker increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Colonoscopy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Corneal abrasion			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Suture related complication			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Motion sickness			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Eye disorders			
Hypotony of eye			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	11		
Conjunctival haemorrhage			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	8		
Dry eye			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	7		
Ocular hypertension			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	9		
Cystoid macular oedema			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Iridocyclitis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Uveitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Vitreous floaters			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Diplopia			

subjects affected / exposed	2 / 30 (6.67%)			
occurrences (all)	2			
Photopsia				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Vitritis				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	2			
Cataract				
subjects affected / exposed	2 / 30 (6.67%)			
occurrences (all)	2			
Chorioretinal folds				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Chromatopsia				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Conjunctival cyst				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Conjunctival granuloma				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Corneal epithelium defect				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Corneal oedema				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Eye irritation				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Eye oedema				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Metamorphopsia				

subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Night blindness				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Keratitis				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Ulcerative keratitis				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	2 / 30 (6.67%)			
occurrences (all)	2			
Dyschromatopsia				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Choroiditis				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Visual field defect				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Optic disc disorder				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Retinal depigmentation				
subjects affected / exposed	6 / 30 (20.00%)			
occurrences (all)	6			
Chalazion				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Punctate keratitis				
subjects affected / exposed	1 / 30 (3.33%)			
occurrences (all)	1			
Retinal haemorrhage				

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eyelid rash			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Acne			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	3		
Dermatitis atopic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blepharitis allergic			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis viral			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Eyelid folliculitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Laryngitis			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infectious mononucleosis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2016	Version number of the Investigational Medicinal Product Dossier (IMPD) updated from 1.0 to 2.0 following approval by the Medicines and Healthcare products Regulatory Agency (MHRA) of requested corrections.
12 May 2016	Version number of the IMPD updated from 2.0 to 3.0 following the addition of supplementary vector stability/potency data required for MHRA approval of a 12-month extension of the AAV2-REP1 vector shelf life to 29 June 2017.
14 December 2016	Version numbers of the Protocol, Participant Information Sheet (PIS) and Informed Consent Form (ICF) updated from 2.0 to 3.0 following MHRA and research ethics committee approval of: • Change of the Principal Investigator at the Moorfields Eye Hospital site. • Amendments and clarifications to the schedule of assessments, and other clarifications in regard to data management for the study.
06 February 2017	Version numbers of the Protocol, PIS and ICF updated from 3.0 to 4.0 following MHRA and research ethics committee approval of amendments to the schedule of assessments (vital signs, immunology, fundus photography and refraction/BVCA).
05 April 2017	Version number of the Protocol updated from 4.0 to 5.0 following MHRA and research ethics committee approval of an amendment to the inclusion criterion specifying that candidates must have BCVA better than or equal to 6/60 (20/200) in the treated eye.
25 May 2017	Version number of the IMPD updated from 3.0 to 4.0 following the addition of supplementary vector stability/potency data required for MHRA approval of a 12-month extension of the AAV2-REP1 vector shelf life to 29 June 2018.
10 November 2017	Version number of the Protocol updated from 5.0 to 6.0 and the version number of the PIS updated from 4.0 to 5.0 following MHRA and research ethics approval of: • Extension of the oral prednisolone course. • Amendment permitting a total volume of no less than 0.2 mL of the AAV2-REP1 vector to be loaded into the injection system. • Amendment to the Conflict of Interest Statement.
12 September 2018	Version number of the Investigator Brochure (IB) updated from 1.0 to 2.0 following MHRA and research ethics committee approval of the inclusion of safety data from other studies (NCT01461213, NCT02077361). Version number of the IMPD updated from 4.0 to 5.0 following the addition of supplementary vector stability/potency data required for MHRA approval of a 12-month extension of the AAV2-REP1 vector shelf life to 29 June 2019.
29 July 2020	Version number of the IB updated from 2.0 to 3.0 following MHRA and research ethics committee approval of the inclusion of clinical data from preceding/parallel studies (NCT01461213, NCT02077361, NCT02553135, NCT02671539), this study (NCT02407678) and studies sponsored by Nightstar Therapeutics (NCT03496012, NCT03507686). The Reference Safety Information now includes "visual acuity reduced" as an expected risk of treatment. Version number of the Protocol updated from 6.0 to 7.0 following following MHRA and research ethics committee approval of updates to the Safety Reporting section to include parameters for determining the clinical significance of changes in BCVA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported