Clinical trial results:
AN OPEN-LABEL DOSE ESCALATION STUDY OF AN ADENO-ASSOCIATED VIRUS VECTOR (AAV2/2-hRPE65p-hRPE65) FOR GENE THERAPY OF SEVERE EARLY-ONSET RETINAL DEGENERATION

Summary

EudraCT number	2006-001571-37
Trial protocol	GB
Global end of trial date	24 July 2014

Results information

Result version number	v1 (current)
This version publication date	26 October 2016
First version publication date	26 October 2016
Summary attachment (see zip file)	Journal Article (Bainbridge et al NEJM.pdf)

Trial information

Trial identification

Sponsor protocol code	AAV2/2-hRPE65p-hRPE65 (UCL 06/061)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00643747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCL
Sponsor organisation address	Gower St, London, United Kingdom, WC1E 6BT
Public contact	Ctimps@ucl.ac.uk, University College London, Gower Street, London, 0044 020 7679 6481, ctimps@ucl.ac.uk
Scientific contact	Professor James Bainbridge Professor Robin Ali UCL Institute of Ophthalmology, UCL Institute of Ophthalmology 11-43 Bath St, London EC1V 9EL, 0044 020 7566 2576, j.bainbridge@ucl.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	30 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2014
Global end of trial reached?	Yes
Global end of trial date	24 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine the efficacy and safety of subretinal administration of a recombinant adeno-associated viral vector (rAAV 2/2.hRPE65p.hRPE65) in individuals with autosomal recessive severe early-onset retinal degeneration due to mutations in RPE65.

Protection of trial subjects:

An important ethical consideration relevant to this study was the application of gene therapy technology for the treatment of a condition that is not life threatening. A gene therapy trial in human subjects should not put subjects at disproportionate risk and for this reason should be restricted to individuals with serious disorders where effective treatments are not available. Although RPE65-related retinal degeneration is not life threatening, there is no effective treatment for the disorder that results inevitably in profound visual impairment. Whilst pre-clinical data suggest that the likelihood of adverse systemic side effects following ocular gene transfer is low, there is a real possibility that this approach will offer a significant benefit in terms of improved visual function and quality of life. The potential risk of gene therapy to existing vision was minimised by restricting intervention to only one eye of each affected individual.

Patients were screened to ensure there were no contra-indications for transient immune suppression, in particular, a history of hypertension, diabetes mellitus, tuberculosis, renal impairment, immunocompromise, osteoporosis, gastric ulceration or severe affective disorder. A detailed assessment of visual function and imaging was performed on both eyes preoperatively. Blood was sampled in order to assess baseline levels of circulating antibodies against AAV2 and RPE65 so that following intervention, immunological responses to vector capsids and transgene product could be determined.

Responses in the first 4 subjects were assessed before subsequent subjects received escalated doses of vector suspension involving larger proportions of the retinal area.

Background therapy:

A standard post-vitrectomy treatment regimen of topical antibiotic (chloramphenicol 0.5% qds for 7 days), steroid (dexamethasone 0.1% qds for 4 weeks) and mydriatic (atropine 1% bd for 7 days) was commenced to minimise inflammation and protect against infection postoperatively.

Subjects were maintained on oral prednisolone for 4 weeks following administration of vector suspension as described above (pre operative procedure).

Evidence for comparator:

No comparator used in the study.

Actual start date of recruitment	01 February 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	5
Adolescents (12-17 years)	3
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects were recruited at Moorfields Eye Hospital between 2007 and 2011. The trial was open label, non-randomised.

Pre-assignment

Screening details:

All subjects recruited had a confirmed diagnosis of severe early-onset retinal degeneration due to missense mutations in the RPE65 gene in the age range 5-30 years.

Period 1

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

Blinding implementation details:

This is not a blinded study.

Arms

Arm title	Intervention

Arm description:

Intraocular administration of recombinant AAV-2 vector encoding the cDNA for human RPE65

Arm type	Experimental
Investigational medicinal product name	rAAV2/2.hRPE65p.hRPE65
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraocular use

Dosage and administration details:

1x10e11vg; 1x10e12 vg

Number of subjects in period 1	Intervention
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	12	12	
Age categorical			
Subjects ranged in age from 6-23 years.			
Units: Subjects			
Children (6-15 years)	6	6	
Adults (16years and older)	6	6	
Gender categorical Units: Subjects			
Female	2	2	
Male	10	10	

End points

End points reporting groups

Reporting group title	Intervention

Reporting group description:

Intraocular administration of recombinant AAV-2 vector encoding the cDNA for human RPE65

Primary: Safety

End point title	Safety[1]

End point description:

The primary safety outcome was the incidence of a grade 3 adverse event at 3 years, defined as either the loss of visual acuity by 15 or more letters on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart or severe unresponsive intraocular inflammation.

End point type	Primary

End point timeframe:

Within 3 years of intervention

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: The primary safety outcome was analysed using descriptive statistics only.

End point values	Intervention			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: events	2			

Attachments (see zip file)	Supplementary data including statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy

End point title	Efficacy

End point description:

The outcomes for efficacy were descriptive in nature and were defined as any improvement in visual function greater than the test–retest variability for any assessment, determined by means of one-way analysis of variance with the use of multiple baseline measurements.

Microperimetry data were analysed using a volumetric approach, Visual Field Modelling and Analysis (VFMA). VFMA can be applied to any static field data where the test locations and associated sensitivity data in dB can be exported. A thin-plate spline is fit through the sensitivity data points and the volume in dB-steradian (dB-sr) is determined by integration of the sensitivity of the visual field with the solid angle beneath the envelope. Test-retest variability was determined by ANOVA.

End point type	Secondary

End point timeframe:

0 - 3 years

End point values	Intervention			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Subjects with improved visual function				

Notes:

[2] - The outcomes for efficacy were primarily descriptive in nature.

Attachments (see zip file)	Supplementary appendix/06-061

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 trial, which was the 3 year follow up visit of the last patient

Adverse event reporting additional description:

Adverse events were recorded for all patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Active treatment

Reporting group description: -

Serious adverse events	Active treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Anaphylactoid reaction	Additional description: Suspected Anaphlactic reaction to anaesthesia (Investigational medicinal product not received.)		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Visual acuity reduced	Additional description: Drop in visual acuityof 22 letters; Drop in visual acuity of 20 letters		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Active treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)		
Investigations			
Weight gain	Additional description: Weight gain		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Lethargy	Additional description: Mild mood disturbance (lethargy) for 2 weeks following procedure; Lethargy		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Dizziness	Additional description: Brief episode of Dizziness		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Leukocytosis	Additional description: Moderately raised white cell count was noted in the first two weeks post surgery		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pain	Additional description: Pain post-surgery; Pain under eyelid of the right eye; Ocular pain after surgery		
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fall	Additional description: Fell onto door handle		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Unwell	Additional description: Unwell		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Th1 response	Additional description: Raised Th1 response.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye disorders			

Intraocular pressure increased	Additional description: Transiently raised IOP, controlled by topical ocular hypotensive; Raised right eye intraocular pressure		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Mucous membrane disorder	Additional description: Small amount of blood stained mucous from Operated eye		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye inflammation	Additional description: 7week post op bilateral Conjunctivitis		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Retinitis	Additional description: Left Retinitis		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Vision blurred	Additional description: Blurry Vision in left eye; Foggy vision		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Uveitis	Additional description: Mild Anterior Uveitis (rebound inflammation after stopping steroid) at 6 weeks post op		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Red right eye	Additional description: slight redness in right eye due to mild knock of right eye.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Visual acuity reduced	Additional description: Drop in visual acuity reduced from 32 to 16 letters		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
irritation	Additional description: irritation to the left eye.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Red left eye	Additional description: Red left eye.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
itchy left eye	Additional description: Slightly Itchy left eye.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Foreign body	Additional description: Foreign body sensation in the left eye.		

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
distorted vision	Additional description: Slight distortion of right vision- not fully resolved, but improving.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea	Additional description: Brief episode of nausea		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Appetite disorder	Additional description: Increased Appetite		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
reflux	Additional description: Gastro-oesophageal reflux		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Additional description: Two episodes of mild-moderate self limiting epistaxis.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cough	Additional description: Cough with green sputum; Cry cough		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Blocked nose	Additional description: Blocked nose		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Cellulitis	Additional description: left upper lid pre-septal cellulitis		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash	Additional description: Rash on right antecubital fossa. Probably related to		

	Ametop application priorto venepuncture (listed side effect of Ametop)		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Acne	Additional description: Flare up of acne like rash on back and arms.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria	Additional description: Urine protein		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia	Additional description: Reduced sleep		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
mood disturbance	Additional description: mood distubrance		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Elevated Mood	Additional description: Elevated Mood on prednisolone		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Glycosuria	Additional description: Trasient Glycosura during prednisolone administration, not associated with hyperglycaemia.		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2009	1. Dose of IMP (rAAV2/2.hRPE65p.hRPE65) increased from 1x1011 DRP/ml to 1x1012 DRP/ml 2. Expansion of inclusion criteria: 2.1 Inclusion of eyes that have visual acuity better than 6/36 Snellen 2.2 Inclusion of subjects with null mutations in the affected gene 2.3 Inclusion of subjects aged 5 years to 7 years of age 3. Reduction of time interval between administration of IMP to consecutive subjects from 8 to 4 weeks 4. Refinement of assessments of visual function 5. Follow up of subjects extended from 1 to 3 years 6. Discontinued long-term flagging of subjects involved in gene therapy since this is no longer required by GTAC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25938638

http://www.ncbi.nlm.nih.gov/pubmed/18441371