



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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 30 January 2009 | <ol style="list-style-type: none">1. Dose of IMP (rAAV2/2.hRPE65p.hRPE65) increased from 1x10¹¹ DRP/ml to 1x10¹² DRP/ml2. Expansion of inclusion criteria:<ol style="list-style-type: none">2.1 Inclusion of eyes that have visual acuity better than 6/36 Snellen2.2 Inclusion of subjects with null mutations in the affected gene2.3 Inclusion of subjects aged 5 years to 7 years of age3. Reduction of time interval between administration of IMP to consecutive subjects from 8 to 4 weeks4. Refinement of assessments of visual function5. Follow up of subjects extended from 1 to 3 years6. 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>