



## Clinical trial results:

### A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301]

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-002109-20 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 06 April 2015  |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v2 (current)   |
| This version publication date     | 15 February 2017   |
| First version publication date    | 05 January 2017  |
| Version creation reason           | <ul style="list-style-type: none"><li>• Changes to summary attachments</li></ul> <p>This update includes a revised synopsis of the clinical study report AAV2-hRPE65v2-301, 13 December 2016. The Amendment 1 has been mainly prepared in order to clarify the study completion date, i.e., the last patient last visit date, 6 April 2015, vs. the final data collection date for primary outcome measure, i.e., the data cut-off date, 16 July 2015. The updates ensured that the date of study completion is aligned with the individual case report forms (CRF).</p> |
| Summary attachment (see zip file) | Clinical Study Report Synopsis (AAV2-hRPE65v2-301_CSR_synopsis_A1.pdf)   |

#### Trial information

##### Trial identification

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | AAV2-hRPE65v2-301 |
|-----------------------|-------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00999609 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Spark Therapeutics, Inc.  |
| Sponsor organisation address | 3737 Market St, Suite 1300, Philadelphia, PA, United States, 19104  |
| Public contact               | Head of Clinical Research and Development, Spark Therapeutics, Inc., 001 888-772-7560, clinicaltrials@sparktx.com |
| Scientific contact           | Head of Clinical Research and Development, Spark Therapeutics, Inc., 001 888-772-7560, clinicaltrials@sparktx.com |

Notes:

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**Paediatric regulatory details**

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|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-001684-PIP01-14 |
| 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:

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**Results analysis stage**

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|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 09 September 2016 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 06 April 2015     |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 06 April 2015     |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this study was to determine whether non-simultaneous, bilateral, subretinal administration of AAV2-hRPE65v2 improves the ability to navigate as measured by mobility testing in adults and children, three years of age or older. Mobility test performance one year following vector administrations was compared to subjects' pre-administration, baseline mobility test performance; independent, masked reviewers were trained to assess ability to navigate.

Protection of trial subjects:

Reviewed trial documents and approved initiation of trial, evaluated progress of trial, made recommendations (as appropriate) to Sponsor, Investigators, IRB, medical monitor regarding continuation/termination of trial based on observed beneficial or adverse effects of the intervention and data review. The Committee included 5 members with expertise in the clinical area and/or clinical trial methodology. Met every 6 months while actively enrolling and then schedule based on safety events and study milestones. All Adverse Events reports and changes to protocol were reviewed by the Committee.

Background therapy:

None

Evidence for comparator:

None; no currently available treatment.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 November 2012 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 15 Years         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 31 |
| Worldwide total number of subjects   | 31                |
| EEA total number of subjects         | 0                 |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                     | 17 |
| Adolescents (12-17 years)                 | 3  |
| Adults (18-64 years)                      | 11 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Potential subjects were recruited from inherited retinal disease centres at two university-based sites (Children's Hospital of Philadelphia and University of Iowa). Subjects were to be aged 3 years or older and have confirmed RPE65 mutations.

### Pre-assignment

Screening details:

Screening included informed consent process, medical and visual history, prior medications, screening for HIV, screening of RPE65 mutations (if adequate records were not available), urine pregnancy test for females of reproductive age, ophthalmic exams with optical coherence tomography (OCT), mobility testing, visual acuity, visual field testing.

### Pre-assignment period milestones

|  |                   |
|--|-------------------|
| Number of subjects started                 | 36 <sup>[1]</sup> |
| Intermediate milestone: Number of subjects | Screened: 36      |
| Intermediate milestone: Number of subjects | Randomized: 31    |
| Number of subjects completed               | 31                |

### Pre-assignment subject non-completion reasons

|                            |                   |
|----------------------------|-------------------|
| Reason: Number of subjects | Screen failure: 5 |
|----------------------------|-------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 36 subjects screened five subjects were considered to be ineligible and were not included in the study.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

Blinding implementation details:

Masked, independent reviewers graded subjects' mobility testing videos, without access to randomization information or any other retinal/visual function test results. The sequence of videos assessments, performed at multiple visits, was also be masked so that the graders did not know whether the video they graded was a baseline evaluation or a follow-up evaluation for any given subject.

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| Arm title                    | Intervention |

Arm description:

AAV2-hRPE65v2 injected to each eye separately

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Adeno-associated viral vector serotype 2 containing the human RPE65 gene |
| Investigational medicinal product code | AAV2-hRPE65v2  |
| Other name                             | voretigene neparvovec (INN)  |
| Pharmaceutical forms                   | Concentrate and solvent for solution for injection                       |
| Routes of administration               | Subretinal use   |

Dosage and administration details:

1.5E11 vector genomes in a volume of 0.3 mL delivered by subretinal injection to each eye sequentially,

no more than 18 days apart

|   |                 |
|---|-----------------|
| <b>Arm title</b>  | Control         |
| Arm description:<br>No intervention, no sham; uninjected control group. |                 |
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm               |                 |

| <b>Number of subjects in period 1</b> | Intervention | Control |
|---------------------------------------|--------------|---------|
| Started                               | 21           | 10      |
| Screened                              | 21           | 10      |
| Randomized                            | 21           | 10      |
| Completed 1 year assessments          | 20           | 9       |
| Completed                             | 20           | 9       |
| Not completed                         | 1            | 1       |
| Physician decision                    | 1            | -       |
| Consent withdrawn by subject          | -            | 1       |

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Intervention |
| Reporting group description:<br>AAV2-hRPE65v2 injected to each eye separately       |              |
| Reporting group title   | Control      |
| Reporting group description:<br>No intervention, no sham; uninjected control group. |              |

| Reporting group values                             | Intervention | Control | Total |
|--|--------------|---------|-------|
| Number of subjects                                 | 21           | 10      | 31    |
| Age categorical                                    |              |         |       |
| Subject age at randomization                       |              |         |       |
| Units: Subjects                                    |              |         |       |
| In utero   | 0            | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0            | 0       | 0     |
| Newborns (0-27 days)                               | 0            | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0            | 0       | 0     |
| Children (2-11 years)                              | 12           | 5       | 17    |
| Adolescents (12-17 years)                          | 3            | 0       | 3     |
| Adults (18-64 years)                               | 6            | 5       | 11    |
| From 65-84 years                                   | 0            | 0       | 0     |
| 85 years and over                                  | 0            | 0       | 0     |
| Age continuous                                     |              |         |       |
| Units: years                                       |              |         |       |
| arithmetic mean                                    | 14.7         | 15.9    |       |
| standard deviation                                 | ± 11.8       | ± 9.5   | -     |
| Gender categorical                                 |              |         |       |
| Units: Subjects                                    |              |         |       |
| Female   | 12           | 6       | 18    |
| Male   | 9            | 4       | 13    |
| Race   |              |         |       |
| Units: Subjects                                    |              |         |       |
| White  | 14           | 7       | 21    |
| Asian  | 3            | 2       | 5     |
| American Indian or Alaska Native                   | 2            | 1       | 3     |
| Black or African American                          | 2            | 0       | 2     |

### Subject analysis sets

|  |                    |
|--|--------------------|
| Subject analysis set title                                   | Efficacy Analysis  |
| Subject analysis set type                                    | Intention-to-treat |
| Subject analysis set description:<br>All randomized subjects |                    |

| Reporting group values                                | Efficacy Analysis |  |  |
|---|-------------------|--|--|
| Number of subjects                                    | 31                |  |  |
| Age categorical                                       |                   |  |  |
| Subject age at randomization                          |                   |  |  |
| Units: Subjects                                       |                   |  |  |
| In utero  | 0                 |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                 |  |  |
| Newborns (0-27 days)                                  | 0                 |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0                 |  |  |
| Children (2-11 years)                                 | 17                |  |  |
| Adolescents (12-17 years)                             | 3                 |  |  |
| Adults (18-64 years)                                  | 11                |  |  |
| From 65-84 years                                      | 0                 |  |  |
| 85 years and over                                     | 0                 |  |  |
| Age continuous  |                   |  |  |
| Units: years  |                   |  |  |
| arithmetic mean                                       | 15.1              |  |  |
| standard deviation                                    | ± 10.9            |  |  |
| Gender categorical                                    |                   |  |  |
| Units: Subjects                                       |                   |  |  |
| Female  | 18                |  |  |
| Male  | 13                |  |  |
| Race  |                   |  |  |
| Units: Subjects                                       |                   |  |  |
| White   | 21                |  |  |
| Asian   | 5                 |  |  |
| American Indian or Alaska Native                      | 3                 |  |  |
| Black or African American                             | 2                 |  |  |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | Intervention       |
| Reporting group description:<br>AAV2-hRPE65v2 injected to each eye separately       |                    |
| Reporting group title   | Control            |
| Reporting group description:<br>No intervention, no sham; uninjected control group. |                    |
| Subject analysis set title  | Efficacy Analysis  |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>All randomized subjects                        |                    |

### Primary: Mobility Testing (Bilateral)

|  |                              |
|--|------------------------------|
| End point title  | Mobility Testing (Bilateral) |
| End point description:<br>The standardized mobility test measures the ability to navigate a randomly selected course layout at different levels of environmental illumination and relates to the subject's extent of visual field and light sensitivity, as well as visual acuity. |                              |
| End point type   | Primary                      |
| End point timeframe:<br>One year (change from baseline)  |                              |

| End point values                            | Intervention    | Control         |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                          | Reporting group | Reporting group |  |  |
| Number of subjects analysed                 | 21              | 10              |  |  |
| Units: Bilateral mobility test change score |                 |                 |  |  |
| arithmetic mean (standard deviation)        | 1.8 (± 1.1)     | 0.2 (± 1)       |  |  |

### Statistical analyses

|   |                                      |
|---|--------------------------------------|
| Statistical analysis title  | Bilateral Mobility Test Change Score |
| Statistical analysis description:<br>Mean change in bilateral mobility testing change score from baseline to 1 year, compared between intervention and control groups |                                      |
| Comparison groups   | Control v Intervention               |
| Number of subjects included in analysis   | 31                                   |
| Analysis specification  | Pre-specified                        |
| Analysis type   | superiority                          |
| P-value   | = 0.001 <sup>[1]</sup>               |
| Method  | Permutation test                     |
| Parameter estimate  | Mean difference (final values)       |
| Point estimate  | 1.6                                  |



|                      |                    |
|----------------------|--------------------|
| Confidence interval  |                    |
| level                | 95 %               |
| sides                | 2-sided            |
| lower limit          | 0.72               |
| upper limit          | 2.41               |
| Variability estimate | Standard deviation |
| Dispersion value     | 1.07               |

Notes:

[1] - Method: permutation test based on Wilcoxon rank-sum.

## Secondary: Full-field light sensitivity threshold (FST) testing: white light

|  |   |
|--|---|
| End point title  | Full-field light sensitivity threshold (FST) testing: white light |
| End point description:   |   |
| Measurable units: Change in Log 10 (cd.s/m2) Log 10 (candela seconds per meter squared). |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| One year (change from baseline)  |   |

| End point values                     | Intervention    | Control         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 21              | 10              |  |  |
| Units: Change in Log 10 (cd.s/m2)    |                 |                 |  |  |
| arithmetic mean (standard deviation) | -2.08 (± 0.29)  | 0.04 (± 0.44)   |  |  |

## Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Full-field Light Sensitivity Threshold Testing |
| Statistical analysis description:  |  |
| Full-field Light Sensitivity Threshold Testing: White Light.   |  |
| Mean change in full-field light sensitivity threshold testing (averaged over both eyes) from baseline to 1 year, compared between intervention and control groups. |  |
| Comparison groups  | Intervention v Control                         |
| Number of subjects included in analysis  | 31   |
| Analysis specification   | Pre-specified                                  |
| Analysis type  | superiority                                    |
| P-value  | < 0.001  |
| Method   | Mixed models analysis                          |
| Parameter estimate   | Mean difference (net)                          |
| Point estimate   | -2.11  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -3.19  |
| upper limit  | -1.04  |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.52                       |

## Secondary: Monocular Mobility Testing

|  |                            |
|--|----------------------------|
| End point title  | Monocular Mobility Testing |
| End point description:<br>Measures the ability to navigate the mobility test using only the assigned first eye |                            |
| End point type   | Secondary                  |
| End point timeframe:<br>One year (change from baseline)  |                            |

| End point values                     | Intervention     | Control          |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 21               | 10               |  |  |
| Units: Mobility test change score    |                  |                  |  |  |
| arithmetic mean (standard deviation) | 1.9 ( $\pm$ 1.2) | 0.2 ( $\pm$ 0.6) |  |  |

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>   | Monocular Mobility Testing     |
| Statistical analysis description:<br>Mean change in monocular mobility testing change score from baseline to 1 year, compared between intervention and control groups |                                |
| Comparison groups   | Intervention v Control         |
| Number of subjects included in analysis   | 31                             |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority <sup>[2]</sup>     |
| P-value   | = 0.001 <sup>[3]</sup>         |
| Method  | Permutation test               |
| Parameter estimate  | Mean difference (final values) |
| Point estimate  | 1.7                            |
| Confidence interval   |                                |
| level   | 95 %                           |
| sides   | 2-sided                        |
| lower limit   | 0.89                           |
| upper limit   | 2.52                           |
| Variability estimate  | Standard deviation             |
| Dispersion value  | 0.89                           |

Notes:

[2] - Parameter type: permutation test based on Wilcoxon rank-sum.

[3] - Method: permutation test based on Wilcoxon rank-sum

## Secondary: Visual Acuity

|                 |               |
|-----------------|---------------|
| End point title | Visual Acuity |
|-----------------|---------------|

End point description:

Measurement of the sharpness of vision, determined by the ability to read letters on a standardized chart from a specified distance. Measured as a change in Logarithm of the minimum angle of resolution (LogMAR).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

One year (change from baseline)

| End point values                     | Intervention    | Control         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 21              | 10              |  |  |
| Units: Change in LogMAR              |                 |                 |  |  |
| arithmetic mean (standard deviation) | -0.16 (± 0.07)  | 0.01 (± 0.1)    |  |  |

## Statistical analyses

|                            |               |
|----------------------------|---------------|
| Statistical analysis title | Visual Acuity |
|----------------------------|---------------|

Statistical analysis description:

Mean change in visual acuity from baseline to 1 year, compared between intervention and control groups.

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | Intervention v Control               |
| Number of subjects included in analysis | 31                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority                          |
| P-value                                 | = 0.17                               |
| Method                                  | Longitudinal repeated measures model |
| Parameter estimate                      | Mean difference (net)                |
| Point estimate                          | -0.16                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.41                                |
| upper limit                             | 0.08                                 |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 0.12                                 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From 15 November 2012 to 6 April 2015

Adverse event reporting additional description:

The safety population (n=29) includes all subjects who received injection in either eye for the intervention group and all control group subjects who did not withdraw, or were not withdrawn, prior to any of the following people knowing the treatment assignment: the subject, parent, Principal Investigator, or Medical Monitor.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 14 |
|--------------------|----|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Intervention |
|-----------------------|--------------|

Reporting group description:

Intervention arm

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description:

Control arm

| Serious adverse events                               | Intervention   | Control       |  |
|--|--|---------------|--|
| Total subjects affected by serious adverse events    |  |               |  |
| subjects affected / exposed                          | 2 / 20 (10.00%)  | 0 / 9 (0.00%) |  |
| number of deaths (all causes)                        | 0  | 0             |  |
| number of deaths resulting from adverse events       | 0  | 0             |  |
| Nervous system disorders                             |  |               |  |
| Convulsion   | Additional description: Associated with pre-existing complex seizure disorder.   |               |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)   | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1  | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0         |  |
| General disorders and administration site conditions |  |               |  |
| Adverse drug reaction                                | Additional description: Associated with pre-existing complex seizure disorder and complications of oral surgery, respectively. |               |  |
| subjects affected / exposed                          | 2 / 20 (10.00%)  | 0 / 9 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2  | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0         |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                                   | Intervention      | Control         |  |
|---|-------------------|-----------------|--|
| Total subjects affected by non-serious adverse events               |                   |                 |  |
| subjects affected / exposed   | 20 / 20 (100.00%) | 9 / 9 (100.00%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                 |  |
| Oral fibroma  |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 0 / 9 (0.00%)   |  |
| occurrences (all)   | 1                 | 0               |  |
| Vascular disorders  |                   |                 |  |
| Hypertension  |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 1 / 9 (11.11%)  |  |
| occurrences (all)   | 1                 | 1               |  |
| General disorders and administration site conditions                |                   |                 |  |
| Chest pain  |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 0 / 9 (0.00%)   |  |
| occurrences (all)   | 1                 | 0               |  |
| Chills  |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 0 / 9 (0.00%)   |  |
| occurrences (all)   | 1                 | 0               |  |
| Facial pain   |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 0 / 9 (0.00%)   |  |
| occurrences (all)   | 1                 | 0               |  |
| Fatigue   |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 0 / 9 (0.00%)   |  |
| occurrences (all)   | 1                 | 0               |  |
| Pain  |                   |                 |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    | 0 / 9 (0.00%)   |  |
| occurrences (all)   | 1                 | 0               |  |
| Pyrexia   |                   |                 |  |
| subjects affected / exposed   | 7 / 20 (35.00%)   | 1 / 9 (11.11%)  |  |
| occurrences (all)   | 9                 | 2               |  |
| Immune system disorders   |                   |                 |  |
| Seasonal allergy  |                   |                 |  |
| subjects affected / exposed   | 0 / 20 (0.00%)    | 1 / 9 (11.11%)  |  |
| occurrences (all)   | 0                 | 1               |  |
| Reproductive system and breast disorders                            |                   |                 |  |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 20 (5.00%)<br>3  | 0 / 9 (0.00%)<br>0  |  |
| Menometrorrhagia<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Menstruation irregular<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders  |                      |                     |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                    | 6 / 20 (30.00%)<br>9 | 1 / 9 (11.11%)<br>1 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 20 (10.00%)<br>2 | 0 / 9 (0.00%)<br>0  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 20 (10.00%)<br>2 | 0 / 9 (0.00%)<br>0  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                       | 6 / 20 (30.00%)<br>6 | 4 / 9 (44.44%)<br>4 |  |
| Psychiatric disorders  |                      |                     |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 20 (0.00%)<br>0  | 1 / 9 (11.11%)<br>2 |  |
| Attention deficit/hyperactivity disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Emetophobia<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 20 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Insomnia   |                      |                     |  |

|  |   |                     |  |
|--|---|---------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0  |  |
| Investigations   |   |                     |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0  |  |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0  |  |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0  |  |
| Electrocardiogram T wave inversion<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Related to the administration procedure               |                     |  |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0  |  |
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Related to the administration procedure in 3 subjects |                     |  |
|  | 4 / 20 (20.00%)<br>5  | 0 / 9 (0.00%)<br>0  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 20 (0.00%)<br>0   | 1 / 9 (11.11%)<br>2 |  |
| Injury, poisoning and procedural complications   |   |                     |  |
| Animal bite<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 20 (10.00%)<br>2  | 0 / 9 (0.00%)<br>0  |  |
| Ankle fracture<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0  |  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 20 (0.00%)<br>0   | 1 / 9 (11.11%)<br>1 |  |
| Eye injury<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 20 (0.00%)<br>0   | 1 / 9 (11.11%)<br>1 |  |
| Foot fracture  |   |                     |  |

|                                      |  |                |  |
|--------------------------------------|--|----------------|--|
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Joint sprain                         |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Laceration                           |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Muscle strain                        |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Cardiac disorders                    |  |                |  |
| Tachycardia                          |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Nervous system disorders             |  |                |  |
| Dizziness                            |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Headache                             | Additional description: Related to administration procedure in one subject |                |  |
| subjects affected / exposed          | 7 / 20 (35.00%)  | 2 / 9 (22.22%) |  |
| occurrences (all)                    | 15   | 5              |  |
| Migraine                             |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Presyncope                           |  |                |  |
| subjects affected / exposed          | 1 / 20 (5.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 1  | 0              |  |
| Syncope                              |  |                |  |
| subjects affected / exposed          | 0 / 20 (0.00%)   | 1 / 9 (11.11%) |  |
| occurrences (all)                    | 0  | 1              |  |
| Blood and lymphatic system disorders |  |                |  |
| Leukocytosis                         | Additional description: Related to use of systemic steroids                |                |  |
| subjects affected / exposed          | 9 / 20 (45.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)                    | 23   | 0              |  |
| Eye disorders                        |  |                |  |



|  |   |                    |
|--|---|--------------------|
| Cataract<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Related to administration procedure   |                    |
|  | 3 / 20 (15.00%)<br>4  | 0 / 9 (0.00%)<br>0 |
| Conjunctival Cyst<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Related to administration procedure   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Eye inflammation<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Related to administration procedure   |                    |
|  | 2 / 20 (10.00%)<br>6  | 0 / 9 (0.00%)<br>0 |
| Eye irritation<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Related to administration procedure   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)                       |   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Eye pruritus<br>subjects affected / exposed<br>occurrences (all)                   |   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Eye swelling<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Related to administration procedure   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Foreign body sensation in eyes<br>subjects affected / exposed<br>occurrences (all) | Additional description: Related to administration procedure   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Iritis<br>subjects affected / exposed<br>occurrences (all)                         |   |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Macular degeneration<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Macular thinning following non-surgical closure of macular hole (below). Related to administration procedure. |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Macular hole<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Resolved to macular thinning (above). Related to administration procedure.                                    |                    |
|  | 1 / 20 (5.00%)<br>1   | 0 / 9 (0.00%)<br>0 |
| Maculopathy  | Additional description: Bilateral epiretinal membrane. Related to administration procedure.   |                    |
|  |   |                    |

|                                 |   |                |  |
|---------------------------------|---|----------------|--|
| subjects affected / exposed     | 1 / 20 (5.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 2   | 0              |  |
| Photopsia                       |   |                |  |
| subjects affected / exposed     | 0 / 20 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)               | 0   | 1              |  |
| Pseudopapilloedema              |   |                |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 1   | 0              |  |
| Retinal haemorrhage             | Additional description: Related to administration procedure |                |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 1   | 0              |  |
| Retinal tear                    | Additional description: Related to administration procedure |                |  |
| subjects affected / exposed     | 2 / 20 (10.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 2   | 0              |  |
| Gastrointestinal disorders      |   |                |  |
| Abdominal distension            |   |                |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 1   | 0              |  |
| Abdominal pain upper            |   |                |  |
| subjects affected / exposed     | 2 / 20 (10.00%)   | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 2   | 0              |  |
| Bowel movement irregularity     |   |                |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 1   | 0              |  |
| Constipation                    |   |                |  |
| subjects affected / exposed     | 1 / 20 (5.00%)  | 0 / 9 (0.00%)  |  |
| occurrences (all)               | 1   | 0              |  |
| Diarrhoea                       |   |                |  |
| subjects affected / exposed     | 2 / 20 (10.00%)   | 1 / 9 (11.11%) |  |
| occurrences (all)               | 2   | 1              |  |
| Gastritis                       |   |                |  |
| subjects affected / exposed     | 0 / 20 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)               | 0   | 1              |  |
| Gastroesophageal reflux disease |   |                |  |
| subjects affected / exposed     | 0 / 20 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)               | 0   | 1              |  |

|   |  |                     |  |
|---|--|---------------------|--|
| Lip pain<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Related to administration procedure                |                     |  |
|   | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
|   |  |                     |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Related to administration procedure in one subject |                     |  |
|   | 6 / 20 (30.00%)<br>9   | 1 / 9 (11.11%)<br>1 |  |
|   |  |                     |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Related to administration procedure in one subject |                     |  |
|   | 8 / 20 (40.00%)<br>9   | 2 / 9 (22.22%)<br>6 |  |
|   |  |                     |  |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)<br><br>Eczema<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all)<br><br>Swelling face<br>subjects affected / exposed<br>occurrences (all) |  |                     |  |
|   | 0 / 20 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
|   |  |                     |  |
|   | 0 / 20 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
|   |  |                     |  |
|   | Additional description: Related to administration procedure                |                     |  |
|   | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
|   |  |                     |  |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Related to administration procedure                |                     |  |
|   | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
|   |  |                     |  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Urine abnormality<br>subjects affected / exposed<br>occurrences (all)  |  |                     |  |
|   | 3 / 20 (15.00%)<br>3   | 1 / 9 (11.11%)<br>1 |  |
|   |  |                     |  |
|   | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)  |  |                     |  |
|   | 0 / 20 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
|   |  |                     |  |
|   | 1 / 20 (5.00%)<br>2  | 0 / 9 (0.00%)<br>0  |  |
|   |  |                     |  |

|   |                      |                     |  |
|---|----------------------|---------------------|--|
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 20 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Infections and infestations   |                      |                     |  |
| Conjunctivitis viral<br>subjects affected / exposed<br>occurrences (all)              | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 20 (5.00%)<br>1  | 1 / 9 (11.11%)<br>1 |  |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 20 (35.00%)<br>9 | 2 / 9 (22.22%)<br>2 |  |
| Pharyngitis streptococcal<br>subjects affected / exposed<br>occurrences (all)         | 1 / 20 (5.00%)<br>2  | 0 / 9 (0.00%)<br>0  |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 20 (10.00%)<br>2 | 3 / 9 (33.33%)<br>3 |  |
| Metabolism and nutrition disorders  |                      |                     |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 20 (5.00%)<br>1  | 0 / 9 (0.00%)<br>0  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 13 January 2014 | Sponsorship of the trial was changed from the Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia to Spark Therapeutics, Inc. This change was described in the 20 August 2013 clinical protocol. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported