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	v1
This version publication date	05 January 2017
First version publication date	05 January 2017
Summary attachment (see zip file)	Clinical Study Report Synopsis (AAV2-hRPE65v2-301_CSR_synopsis.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:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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:

Results analysis stage

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:

General information about the trial

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:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	31
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)	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[1]
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

Arm title	Control
Arm description: No intervention, no sham; uninjected control group.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	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:	
AAV2-hRPE65v2 injected to each eye separately	
Reporting group title	Control
Reporting group description:	
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:	
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 (gestational age < 37 wks)	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 65-84 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: AAV2-hRPE65v2 injected to each eye separately	
Reporting group title	Control
Reporting group description: No intervention, no sham; uninjected control group.	
Subject analysis set title	Efficacy Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized subjects	

Primary: Mobility Testing (Bilateral)

End point title	Mobility Testing (Bilateral)
End point description: 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: 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: Mean change in bilateral 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
P-value	= 0.001 [1]
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:

Measures the ability to navigate the mobility test using only the assigned first eye

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: Mobility test change score				
arithmetic mean (standard deviation)	1.9 (± 1.2)	0.2 (± 0.6)		

Statistical analyses

Statistical analysis title	Monocular Mobility Testing

Statistical analysis description:

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[2]
P-value	= 0.001 [3]
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 %

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

subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram T wave inversion	Additional description: Related to the administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Intraocular pressure increased	Additional description: Related to the administration procedure in 3 subjects		
subjects affected / exposed	4 / 20 (20.00%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Ankle fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Excoriation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Eye injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	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	Additional description: Related to administration procedure		
subjects affected / exposed	3 / 20 (15.00%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Conjunctival Cyst	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye inflammation	Additional description: Related to administration procedure		
subjects affected / exposed	2 / 20 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Eye irritation	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye swelling	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Foreign body sensation in eyes	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Iritis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Macular degeneration	Additional description: Macular thinning following non-surgical closure of macular hole (below). Related to administration procedure.		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Macular hole	Additional description: Resolved to macular thinning (above). Related to administration procedure.		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	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	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nausea	Additional description: Related to administration procedure in one subject		
subjects affected / exposed	6 / 20 (30.00%)	1 / 9 (11.11%)	
occurrences (all)	9	1	
Vomiting	Additional description: Related to administration procedure in one subject		
subjects affected / exposed	8 / 20 (40.00%)	2 / 9 (22.22%)	
occurrences (all)	9	6	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rash	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Swelling face	Additional description: Related to administration procedure		
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 20 (15.00%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Urine abnormality			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported