



Clinical trial results:

A Multiple-Site, Phase 2, Safety and Efficacy Trial of a Recombinant Adeno-associated Virus Vector Expressing Alpha 1 Antitrypsin (rAAV1-CB-hAAT) in Patients with Alpha 1 Antitrypsin Deficiency

Summary

EudraCT number	2009-014286-20
Trial protocol	IE
Global end of trial date	01 October 2015

Results information

Result version number	v1
This version publication date	28 February 2019
First version publication date	28 February 2019

Trial information

Trial identification

Sponsor protocol code	AGTC-AAT-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01054339
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Applied Genetic Technologies Corporation
Sponsor organisation address	14193 NW 119th Terrace, Suite 10, Alachua, United States, 32615
Public contact	Ellery Mangas, Executive Director, Regulatory Affairs, Applied Genetic Technologies Corporation, 386 5185526, emangas@agtc.com
Scientific contact	Ellery Mangas, Executive Director, Regulatory Affairs, Applied Genetic Technologies Corporation, 386 5185526, emangas@agtc.com

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	14 September 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2011
Global end of trial reached?	Yes
Global end of trial date	01 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the safety and efficacy of intramuscular (IM) administration of a recombinant adenoassociated virus (rAAV) alpha-1 antitrypsin (AAT) vector (rAAV1-CB-hAAT) in AAT-deficient adults at three dosage levels [6.0×10^{11} , 1.9×10^{12} and 6.0×10^{12} vector genome particles (vg) per kg body weight].

Protection of trial subjects:

This study was conducted in full conformity with the current revision of the Declaration of Helsinki, or with ICH GCP regulations and guidelines, whichever affords the greater protection to the subject.

This study was reviewed and approved by an appropriate IRB/EC of this protocol, the associated informed consent documents, and other materials were provided to potential study participants. All amendments to the protocol, consent documents or associated materials were approved before they are placed into use.

The medical history and physical examination performed during the screening visit identified individuals with medical conditions that would increase the risks associated with participation in the study. Results of all laboratory and safety evaluations were reviewed by the investigators and sponsor throughout the trial, and a Data and Safety Monitoring Board (DSMB) reviewed safety data from completed study cohorts before enrollment into subsequent study cohorts. Informed consent was required for participation. There was at least a 2-week interval between administration of study agent to participants within each cohort and at least a 3-week interval between administration of study agent to the last participant in a cohort and the first participant in the next cohort.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 March 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from two clinical trial sites (University of Massachusetts Medical Center and Cincinnati Children's Hospital Medical Center).

Pre-assignment

Screening details:

Subjects were recruited from two clinical trial sites (University of Massachusetts Medical Center and Cincinnati Children's Hospital Medical Center).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Low Dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	rAAV1-CB-hAAT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

6 x 10e11 vg/kg administered as 10 IM injections distributed across a single muscle site

Arm title	Middle Dose
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	rAAV1-CB-hAAT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1.9 x 10e12 vg/kg administered as 32 IM injections distributed across three muscle sites

Arm title	High Dose
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	rAAV1-CB-hAAT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

6 x 10e12 vg/kg administered as 100 IM injections distributed across 10 muscle sites

Number of subjects in period 1	Low Dose	Middle Dose	High Dose
Started	3	3	3
Completed	3	3	3

Baseline characteristics

Reporting groups

Reporting group title	Low Dose
Reporting group description: -	
Reporting group title	Middle Dose
Reporting group description: -	
Reporting group title	High Dose
Reporting group description: -	

Reporting group values	Low Dose	Middle Dose	High Dose
Number of subjects	3	3	3
Age categorical			
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	3	3
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	50.3	48.7	54.3
standard deviation	± 26.4	± 9.3	± 3.5
Gender categorical			
Units: Subjects			
Female	3	2	2
Male	0	1	1
Alpha-1 antitrypsin phenotype			
Measure Description: Alpha-1 antitrypsin phenotype determined by isoelectric focusing gel electrophoresis			
Units: Subjects			
ZZ	2	3	3
SZ	1	0	0
Serum total alpha-1 antitrypsin concentration			
For serum total AAT, ANOVA showed that there was no significant effect of dose, no significant effect of change over time, and no significant interaction between dose and time			
Units: micromole(s)/litre			
arithmetic mean	6.65	3.54	3.45
standard deviation	± 2.00	± 0.12	± 0.25

Reporting group values	Total		
Number of subjects	9		

Age categorical			
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)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	8		
From 65-84 years	1		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	7		
Male	2		
Alpha-1 antitrypsin phenotype			
Measure Description: Alpha-1 antitrypsin phenotype determined by isoelectric focusing gel electrophoresis			
Units: Subjects			
ZZ	8		
SZ	1		
Serum total alpha-1 antitrypsin concentration			
For serum total AAT, ANOVA showed that there was no significant effect of dose, no significant effect of change over time, and no significant interaction between dose and time			
Units: micromole(s)/litre			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Low Dose
Reporting group description: -	
Reporting group title	Middle Dose
Reporting group description: -	
Reporting group title	High Dose
Reporting group description: -	

Primary: Frequency of Grade 3 or 4 Adverse Events

End point title	Frequency of Grade 3 or 4 Adverse Events ^[1]
End point description:	
Analysis based on all subjects enrolled in study	
End point type	Primary
End point timeframe:	
During 1 year after study agent administration	

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: N/A

End point values	Low Dose	Middle Dose	High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: Number of occurrences	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Serum M-specific Alpha-1 Antitrypsin Concentration

End point title	Changes in Serum M-specific Alpha-1 Antitrypsin Concentration
End point description:	
The change in serum M-specific alpha-1 antitrypsin concentration was calculated as the difference between the mean values at the screening and baseline visits and the mean values at the 6, 9 and 12 month visits. The standard error of the difference was calculated as the square root ($s1^2/n1 + s2^2/n2$), where s1 is the standard deviation of the baseline mean, s2 is the standard deviation of the month 6-12 mean, n1 is the number of baseline values and n2 is the number of month 6-12 values.	
End point type	Secondary
End point timeframe:	
During months 6-12 after study agent administration.	

End point values	Low Dose	Middle Dose	High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	3	
Units: nanomolar				
arithmetic mean (standard error)	31.5 (± 7.56)	71.8 (± 22.73)	239.2 (± 27.57)	

Statistical analyses

Statistical analysis title	Serum M-specific AAT measures analysis of variance
Statistical analysis description:	
For serum M-specific AAT, ANOVA showed that there was a significant effect of dose, a significant change over time, and a significant interaction between dose and time	
Comparison groups	Low Dose v Middle Dose v High Dose
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.0001
Method	ANOVA
Parameter estimate	Mean difference (final values)

Notes:

[2] - Vector-mediated expression of AAT was monitored using assays for M-specific AAT concentration measured by ELISA, total AAT concentration measured by nephelometry, and AAT phenotype measured by isoelectric focusing (IEF).

Secondary: Changes in Serum Total Alpha-1 Antitrypsin Concentrations

End point title	Changes in Serum Total Alpha-1 Antitrypsin Concentrations
End point description:	
The change in serum total alpha-1 antitrypsin concentration was calculated as the difference between the mean values at the screening and baseline visits and the mean values at the 6, 9 and 12 month visits. The standard error of the difference was calculated as square root ($s1^2/n1 + s2^2/n2$), where s1 is the standard deviation of the baseline mean, s2 is the standard deviation of the month 6-12 mean, n1 is the number of baseline values and n2 is the number of month 6-12 values.	
End point type	Secondary
End point timeframe:	
During months 6-12 after study agent administration.	

End point values	Low Dose	Middle Dose	High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: micromolar				
arithmetic mean (standard error)	0.33 (± 1.14)	0.16 (± 0.10)	0.19 (± 0.16)	

Statistical analyses

Statistical analysis title	Serum total AAT measures analysis of variance
Statistical analysis description:	
For serum total AAT, ANOVA showed that there was no significant effect of dose, no significant effect of change over time, and no significant interaction between dose and time	
Comparison groups	Middle Dose v High Dose v Low Dose
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1524
Method	ANOVA
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 year

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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Reporting groups

Reporting group title	Low Dose
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Reporting group description:

rAAV1-CB-hAAT at dosage level of 6 x 10e11 vg/kg administered as 10 IM injections distributed across a single muscle site

Reporting group title	Middle Dose
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Reporting group description:

rAAV1-CB-hAAT at dosage level of 1.9 x 10e12 vg/kg administered as 32 IM injections distributed across three muscle sites

Reporting group title	High Dose
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Reporting group description:

rAAV1-CB-hAAT at dosage level of 6 x 10e12 vg/kg administered as 100 IM injections distributed across 10 muscle sites

Serious adverse events	Low Dose	Middle Dose	High Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Diverticulitis	Additional description: A 51 y/o man received high dose of study drug on 5 Oct 2010, diverticulitis diagnosed on 14 Mar 2011, admitted to hospital, treated with antibiotics and symptoms resolved. The adverse event was considered not related to study agent.		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Low Dose	Middle Dose	High Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)

Vascular disorders	Ecchymosis			
	subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	occurrences (all)	1	1	0
	Phlebitis superficial	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
	subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	occurrences (all)	1	1	0
Aortic aneurysm	subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	occurrences (all)	0	1	0
	Orthostatic hypotension			
	subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
	Postmastectomy lymphoedema syndrome			
	subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
	occurrences (all)	1	0	0
General disorders and administration site conditions	Injection site discomfort	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
	subjects affected / exposed	2 / 3 (66.67%)	2 / 3 (66.67%)	2 / 3 (66.67%)
	occurrences (all)	2	2	2
	Influenza-like illness	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
	subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
	Injection site atrophy	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
	subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	occurrences (all)	0	1	0
	Injection site erythema	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
	subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
	occurrences (all)	0	1	0
	Injection site pain	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		

	than 1 subject in the study.		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Malaise	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Post-procedural discomfort	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Injection site haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	3 / 3 (100.00%)	3 / 3 (100.00%)
occurrences (all)	1	3	3
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Lung neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Throat irritation			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Investigations Blood creatine phosphokinase increased alternative assessment type: Systematic subjects affected / exposed occurrences (all)	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study. One other		
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	3 / 3 (100.00%) 3
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Post procedural oedema subjects affected / exposed occurrences (all) Post procedural haematoma subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 3 / 3 (100.00%) 3	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1	0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all) Anosmia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
	0 / 3 (0.00%) 0	2 / 3 (66.67%) 2	0 / 3 (0.00%) 0
	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0

Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hiatus hernia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue			

disorders			
Muscle spasms	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Muscle strain	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Muscle twitching	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Bone lesion	Additional description: Joint sprain		
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Limb discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Ear infection	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Upper respiratory infection	Additional description: Because of small sample size, adverse events are listed only for (1) those considered possibly, probably or definitely related to study agent or study agent administration procedures, or (2) that occurred in more than 1 subject in the study.		
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	1	2
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gingival abscess			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study results based on small number of subjects.
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/21609134>

<http://www.ncbi.nlm.nih.gov/pubmed/24231351>

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