Clinical trial results:
A Multicenter, Open-label Study of SI-6603 in Patients with Lumbar Disc Herniation (Phase III)

Summary

EudraCT number	2014-001449-26
Trial protocol	ES DE
Global end of trial date	21 February 2018

Results information

Result version number	v1 (current)
This version publication date	12 May 2019
First version publication date	12 May 2019

Trial information

Trial identification

Sponsor protocol code	6603/1132

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02421601
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seikagaku Corporation
Sponsor organisation address	6-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo , Japan, 100-0005
Public contact	Clinical Development Department, Seikagaku Corporation, +81 3-5220-8948,
Scientific contact	Clinical Development Department, Seikagaku Corporation, +81 3-5220-8948,

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	21 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to evaluate the safety of a single-dose intervertebral disc injection of SI-6603 at a dose of 1.25 U in subjects with lumbar disc herniation, for a 26-week follow-up period.

Protection of trial subjects:

At each study center, the protocol and informed consent form (ICF) for this study were reviewed and approved by a duly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC) before subjects were screened for entry. Amendments to the protocol were reviewed and approved in the same manner before being implemented. This study was designed and monitored in accordance with the CRO's standard operating procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major Regulatory Authorities, and in accordance with the Declaration of Helsinki as amended by the 52nd General Assembly in October 2013. Informed consent was obtained from each subject (or subject's legally authorized representative) before the subject was admitted to the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 25
Country: Number of subjects enrolled	Spain: 75
Country: Number of subjects enrolled	Germany: 72
Country: Number of subjects enrolled	United States: 839
Worldwide total number of subjects	1011
EEA total number of subjects	172

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	957
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was planned to be conducted at approximately 80 study centers in the United States (US) and European Union (EU). In the US there were 39 study centers initiated and 33 enrolled subjects. In the EU there were 27 study centers initiated: 9 in Germany, 14 in Spain, and 4 in Romania, with 7, 10, and 4 centers enrolling subjects, respectively

Pre-assignment

Screening details:

The study consisted of a 4-week Screening period (Days -28 to -1). All other assessments were done at Screening as per the Schedule of Procedures and Assessments.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SI-6603 (US)

Arm description:

Following a 4-week Screening period, on Day 0 all subjects in US received a single intradiscal injection of SI-6603 1.25 U.

Arm type	Experimental
Investigational medicinal product name	SI-6603
Investigational medicinal product code	SI-6603
Other name	Condoliase
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradiscal use

Dosage and administration details:

SI-6603 for injection is a lyophilized injectable containing SI-6603 as an active ingredient. An SI-6603 for injection vial was reconstituted with 1.2 mL of saline to prepare a 1.25 U/mL solution of SI-6603. A volume of 1.0 mL was administered into the intervertebral disc in a single-dose.

Arm title	SI-6603 (EU)

Arm description:

Following a 4-week Screening period, on Day 0 all subjects in Germany, Spain and Romania received a single intradiscal injection of SI-6603 1.25 U.

Arm type	Experimental
Investigational medicinal product name	SI-6603
Investigational medicinal product code	SI-6603
Other name	Condoliase
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradiscal use

Dosage and administration details:

SI-6603 for injection is a lyophilized injectable containing SI-6603 as an active ingredient. An SI-6603 for injection vial was reconstituted with 1.2 mL of saline to prepare a 1.25 U/mL solution of SI-6603. A volume of 1.0 mL was administered into the intervertebral disc in a single-dose.

Number of subjects in period 1	SI-6603 (US)	SI-6603 (EU)
Started	839	172
Completed	753	156
Not completed	86	16
Adverse event, serious fatal	4	-
Consent withdrawn by subject	29	7
Physician decision	3	1
Adverse event, non-fatal	1	-
Other	45	7
Lack of efficacy	4	1

Baseline characteristics

Reporting groups	
Reporting group title	SI-6603 (US)
Reporting group description:	
Following a 4-week Screening period, on Day 0 all subjects in US received a single intradiscal injection of SI-6603 1.25 U.	
Reporting group title	SI-6603 (EU)
Reporting group description:	
Following a 4-week Screening period, on Day 0 all subjects in Germany, Spain and Romania received a single intradiscal injection of SI-6603 1.25 U.	

Reporting group values	SI-6603 (US)	SI-6603 (EU)	Total
Number of subjects	839	172	1011
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	49.7	46.1	
inter-quartile range (Q1-Q3)	43.0 to 57.0	39.0 to 52.5	-
Gender categorical			
Units: Subjects			
Female	376	83	459
Male	463	89	552

End points

End points reporting groups

Reporting group title	SI-6603 (US)
Reporting group description:	
Following a 4-week Screening period, on Day 0 all subjects in US received a single intradiscal injection of SI-6603 1.25 U.	
Reporting group title	SI-6603 (EU)
Reporting group description:	
Following a 4-week Screening period, on Day 0 all subjects in Germany, Spain and Romania received a single intradiscal injection of SI-6603 1.25 U.	

Primary: Number of subjects with Adverse events (AEs)

End point title	Number of subjects with Adverse events (AEs)[1]
End point description:	
The number of subjects with AEs was presented as a measure to evaluate the safety of a single-dose intervertebral disc injection of SI-6603 at a dose of 1.25 U in patients with lumbar disc herniation.	
End point type	Primary
End point timeframe:	
From screening (Day -28) to follow-up period (week 26) or early discontinuation. Although AEs were collected from Day -28, only those AEs collected from Day 0 to week 26 or early discontinuation are presented in results.	

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: No statistical analysis is available for this primary endpoint

End point values	SI-6603 (US)	SI-6603 (EU)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	824	167		
Units: Subjects				
number (not applicable)				
Any Treatment-Emergent Adverse Events (TEAE)	497	118		
Any treatment-related TEAE	140	39		
Any serious adverse event (SAE)	31	5		
Any treatment-related SAE	0	0		
TEAE with fatal outcome	4	0		
Severe TEAE	31	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening (Day -28) to follow-up period (week 26) or early discontinuation.
Although AEs were collected from Day -28, only those AEs collected from Day 0 to week 26 or early discontinuation are presented in results.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SI-6603 (US)

Reporting group description:

Following a 4-week Screening period, on Day 0 all subjects in US received a single intradiscal injection of SI-6603 1.25 U.

Reporting group title	SI-6603 (EU)

Reporting group description:

Following a 4-week Screening period, on Day 0 all subjects in Germany, Spain and Romania received a single intradiscal injection of SI-6603 1.25 U.

Serious adverse events	SI-6603 (US)	SI-6603 (EU)	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 824 (3.76%)	5 / 167 (2.99%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease recurrent			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine adenocarcinoma			

subjects affected / exposed	0 / 824 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 824 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	2 / 824 (0.24%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 824 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 824 (0.24%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug dependence			

subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Nuclear magnetic resonance imaging abnormal			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 824 (0.24%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	2 / 824 (0.24%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 824 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 824 (0.24%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 824 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 824 (0.24%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraspinal abscess			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 824 (0.12%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SI-6603 (US)	SI-6603 (EU)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	493 / 824 (59.83%)	117 / 167 (70.06%)	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	7 / 824 (0.85%)	2 / 167 (1.20%)	
occurrences (all)	8	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 824 (1.09%)	0 / 167 (0.00%)	
occurrences (all)	9	0	
Blood cholesterol increased			
subjects affected / exposed	4 / 824 (0.49%)	2 / 167 (1.20%)	
occurrences (all)	4	2	
Blood triglycerides increased			
subjects affected / exposed	10 / 824 (1.21%)	0 / 167 (0.00%)	
occurrences (all)	11	0	
C-reactive protein increased			
subjects affected / exposed	37 / 824 (4.49%)	3 / 167 (1.80%)	
occurrences (all)	40	3	
Nuclear magnetic resonance imaging spinal abnormal			
subjects affected / exposed	158 / 824 (19.17%)	48 / 167 (28.74%)	
occurrences (all)	158	49	
Spinal X-ray abnormal			
subjects affected / exposed	64 / 824 (7.77%)	12 / 167 (7.19%)	
occurrences (all)	71	14	
White blood cell count increased			
subjects affected / exposed	12 / 824 (1.46%)	0 / 167 (0.00%)	
occurrences (all)	13	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 824 (0.24%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
Hand fracture			
subjects affected / exposed	0 / 824 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 824 (1.09%)	0 / 167 (0.00%)	
occurrences (all)	9	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 824 (0.24%)	2 / 167 (1.20%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	8 / 824 (0.97%)	6 / 167 (3.59%)	
occurrences (all)	8	6	
Hypoaesthesia			
subjects affected / exposed	6 / 824 (0.73%)	3 / 167 (1.80%)	
occurrences (all)	8	4	
Paraesthesia			
subjects affected / exposed	1 / 824 (0.12%)	6 / 167 (3.59%)	
occurrences (all)	1	6	
Sciatica			
subjects affected / exposed	22 / 824 (2.67%)	4 / 167 (2.40%)	
occurrences (all)	23	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 824 (0.00%)	2 / 167 (1.20%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 824 (0.85%)	2 / 167 (1.20%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	12 / 824 (1.46%)	3 / 167 (1.80%)	
occurrences (all)	12	3	
Vomiting			
subjects affected / exposed	5 / 824 (0.61%)	2 / 167 (1.20%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 824 (0.36%)	2 / 167 (1.20%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			

subjects affected / exposed	3 / 824 (0.36%)	2 / 167 (1.20%)	
occurrences (all)	3	2	
Pruritus			
subjects affected / exposed	3 / 824 (0.36%)	2 / 167 (1.20%)	
occurrences (all)	3	2	
Rash			
subjects affected / exposed	11 / 824 (1.33%)	0 / 167 (0.00%)	
occurrences (all)	12	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 824 (2.18%)	6 / 167 (3.59%)	
occurrences (all)	18	6	
Back pain			
subjects affected / exposed	128 / 824 (15.53%)	29 / 167 (17.37%)	
occurrences (all)	136	32	
Intervertebral disc protrusion			
subjects affected / exposed	3 / 824 (0.36%)	2 / 167 (1.20%)	
occurrences (all)	3	2	
Muscle spasms			
subjects affected / exposed	16 / 824 (1.94%)	1 / 167 (0.60%)	
occurrences (all)	19	1	
Neck pain			
subjects affected / exposed	3 / 824 (0.36%)	2 / 167 (1.20%)	
occurrences (all)	3	3	
Pain in extremity			
subjects affected / exposed	42 / 824 (5.10%)	11 / 167 (6.59%)	
occurrences (all)	42	11	
Infections and infestations			
Influenza			
subjects affected / exposed	6 / 824 (0.73%)	4 / 167 (2.40%)	
occurrences (all)	6	4	
Nasopharyngitis			
subjects affected / exposed	9 / 824 (1.09%)	11 / 167 (6.59%)	
occurrences (all)	9	13	
Sinusitis			

subjects affected / exposed	12 / 824 (1.46%)	1 / 167 (0.60%)	
occurrences (all)	13	1	
Tonsillitis			
subjects affected / exposed	0 / 824 (0.00%)	3 / 167 (1.80%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	9 / 824 (1.09%)	1 / 167 (0.60%)	
occurrences (all)	9	1	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	13 / 824 (1.58%)	1 / 167 (0.60%)	
occurrences (all)	14	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2015	Amendment 1 included the following changes to the protocol: •Change in administrative details: new General Manager at Seikagaku and a change in the name of the company used for imaging •Per-protocol population was removed, as there was no primary efficacy analysis •Clarification was added to an exclusion criterion •Criteria were modified for subject withdrawal, to allow a more appropriate evaluation of safety •The definition of permitted concomitant medications and previous and concomitant therapies were clarified •Notes for precaution on intradiscal injection was added •Subject demographic parameters were clarified
09 September 2015	Amendment 2 included the following changes to the protocol: •Planned number of study centers were modified •Follow-up period increased from 13 to 26 weeks •Clarification was added to the exclusion criteria •A Data Safety Monitoring Board was established
24 June 2016	Amendment 3 included the following changes to the protocol: •Changes in measuring method and research center of a laboratory assessment •The SAE reporting contact was changed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported