Clinical trial results:
Prospective, randomised, open label, multicentre Phase II clinical trial to investigate the efficacy and safety of the treatment of large defects (4-10 cm2) with 3 different doses of the autologous chondrocyte transplantation product co.don chondrosphere® (ACT3D-CS) in subjects with cartilage defects of the knee

Summary

EudraCT number	2009-016816-20
Trial protocol	DE
Global end of trial date	31 March 2018

Results information

Result version number	v1 (current)
This version publication date	13 November 2019
First version publication date	13 November 2019
Summary attachment (see zip file)	cod16 HS14 Study Synopse (Synopse_cod_16_HS_14_study_report_FU60_eudract.pdf)

Trial information

Trial identification

Sponsor protocol code	cod16HS14

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	co.don AG
Sponsor organisation address	Warthestr. 21, Teltow, Germany, 14513
Public contact	co.don AG, co.don AG, 0049 30240352361 , i.oefler@codon.de
Scientific contact	co.don AG, co.don AG, 0049 30240352361, i.oefler@codon.de

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	12 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

General Objectives:
Assessment of the short-term and long-term efficacy and safety of 3 different doses of the three-dimensional autologous chondrocyte transplantation product ACT3D-CS for the treatment of cartilage defects (≥ 4-10 cm2) of knee joints.

The health economic outcomes are mainly intended to be assessed and evaluated as a basis for future negotiations with health insurances, health care providers and development of newly implemented procedural codes within the German DRG (Diagnosis Related Groups) system for ACT3D-CS.
Health economic data within the phase II study will be collected and assessed, where different doses of ACT3D-CS will be applied.

Primary Objectives:
Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) from baseline (Day 0) to final assessment (FA) at 12 months after transplantation determined for each dosage group and between the dosage groups

Protection of trial subjects:

In case of pain, patient agreed only to use paracetamol mono- (maximum 4 g/day) or a combination preparation and oral and/or topical NSAIDs during the trial and to discontinue the use of oral and/or topical NSAIDs and/or paracetamol combination preparation 1 week before each visit (whereby the use of paracetamol mono-preparation, maximum 4 g/day was allowed). However, in the morning of the visit day, no pain medication was allowed. Other pain medications were allowed during the surgical procedure and could be taken for a period not exceeding 4 weeks after surgery.
Any illness of the patient present at the time of enrolment into the trial was considered as concomitant illness and documented in the Concomitant Illness & Medication/Measure Form of the eCRFs containing the following:
– Concomitant illness
– Medication/Measure
– Medication form
– Dosing/Frequency
– Start date
– Stop date
Every concomitant illness (except for those constituting exclusion criteria as defined in Section 9.3.2) was examined before the patient's enrolment into the trial and treated with an appropriate medication/measure if necessary. Any illness emerging during the course of the trial was to be regarded as an adverse event (see Section 9.5.1.3.1).
All illnesses and any surgical treatment of the patient and medications taken / measures performed during the six months before enrolment into the trial were also to be documented in the Concomitant Illness & Medication/Measure Form.
Any medication/measure (including over-the-counter medication, multi-vitamin or nutritional supplement) taken by the patient or prescribed during the trial was to be recorded in the Concomitant Illness & Medication/Measure Form of the eCRFs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	75
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place from October 2010 to December 2014 in the participating centers.

Pre-assignment

Screening details:

All patients with cartilage defects consulting the investigator during the recruitment phase of this clinical trial were informed of the trial. Patients who were interested in study participation, and had carefully read the Patient Information and signed and dated the Patient Informed Consent form, were screened for eligibility.

Period 1

Period 1 title	Day before arthroscopy
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Enrolled Patients
Arm description: -	
Arm type	Arthroscopy for biopsy
Investigational medicinal product name	Spherox implantation suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution and suspension for suspension for injection in pre-filled syringe
Routes of administration	Intraarticular use

Dosage and administration details:

Arthroscopy for cartilage biopsy

Number of subjects in period 1	Enrolled Patients
Started	75
Completed	75

Period 2

Period 2 title	overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Patients with defect sizes between ≥4 cm2 and 10 cm2 were assigned to autologous chondrocyte implantation with three different dose levels of the three-dimensional product chondrosphere:
Group A: chondrosphere, 3–7 spheroids/cm2

Arm type	Experimental
Investigational medicinal product name	Spherox implantation suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution and suspension for suspension for injection in pre-filled syringe
Routes of administration	Intraarticular use

Dosage and administration details:

Once: arthroscopic administration of a dose of 3-7 spheroids per square cm

Arm title	Group B

Arm description:

Patients with defect sizes between ≥4 cm2 and 10 cm2 were assigned to autologous chondrocyte implantation with three different dose levels of the three-dimensional product chondrosphere:
Group B: chondrosphere, 10–30 spheroids/cm2

Arm type	Experimental
Investigational medicinal product name	Spherox implantation suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution and suspension for suspension for injection in pre-filled syringe
Routes of administration	Intraarticular use

Dosage and administration details:

Once: arthroscopic administration of 10-30 spheroids per square cm

Arm title	Group C

Arm description:

Patients with defect sizes between ≥4 cm2 and 10 cm2 were assigned to autologous chondrocyte implantation with three different dose levels of the three-dimensional product chondrosphere:
Group C: chondrosphere, 40–70 spheroids/cm2

Arm type	Experimental
Investigational medicinal product name	Spherox implantation suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution and suspension for suspension for injection in pre-filled syringe
Routes of administration	Intraarticular use

Dosage and administration details:

Once: arthroscopic administration of 40-70 spheroids per square cm

Number of subjects in period 2	Group A	Group B	Group C
Started	25	25	25
Completed	17	20	11
Not completed	8	5	14
Consent withdrawn by subject	2	2	3
Physician decision	-	-	1
Adverse event, non-fatal	-	-	2
Pregnancy	1	1	1
Preexisting bone cyst worsening	1	-	-
Lost to follow-up	3	2	4
Protocol deviation	1	-	3

Baseline characteristics

End points

End points reporting groups

Reporting group title	Enrolled Patients
Reporting group description: -	
Reporting group title	Group A
Reporting group description:	
Patients with defect sizes between ≥4 cm2 and 10 cm2 were assigned to autologous chondrocyte implantation with three different dose levels of the three-dimensional product chondrosphere: Group A: chondrosphere, 3–7 spheroids/cm2	
Reporting group title	Group B
Reporting group description:	
Patients with defect sizes between ≥4 cm2 and 10 cm2 were assigned to autologous chondrocyte implantation with three different dose levels of the three-dimensional product chondrosphere: Group B: chondrosphere, 10–30 spheroids/cm2	
Reporting group title	Group C
Reporting group description:	
Patients with defect sizes between ≥4 cm2 and 10 cm2 were assigned to autologous chondrocyte implantation with three different dose levels of the three-dimensional product chondrosphere: Group C: chondrosphere, 40–70 spheroids/cm2	

Primary: Overall KOOS

End point title	Overall KOOS
End point description:	
End point type	Primary
End point timeframe:	
baseline (Day 0) and 6 weeks, 3 months, 6 months, 12 months (final assessment) and follow-up Visits 5–9 (18, 24, 36, 48 and 60 months) after implantation	

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[1]	25	24[2]	
Units: 0-100	23	25	24	

Notes:

[1] - 1 patient not treated due to insufficient cell growth, 1 patient did not complete KOOS at baseline

[2] - 1 patient was not treated due to insufficient cell growth

Attachments (see zip file)	Overall KOOS and change in overall

Statistical analyses

Statistical analysis title	Primary Efficacy Data for ITT-Population
Comparison groups	Group B v Group A v Group C

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.05 [4]
Method	t-test, 2-sided

Notes:

[3] - The change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score) at 12 months from baseline (Day 0) was tested statistically for all three dose groups by applying the principle of ordered hypotheses. The statistical hypothesis per dose group was equality of the overall KOOS at 12 months compared with baseline versus the alternative of superiority.

[4] - The null hypothesis to be tested in the primary analysis was:
H0: delta = KOOSV12 - KOOSBase = 0
It was to be rejected if p < or = alpha = 0.05 in a one-sample, two-sided t test (for details see Section 6.4.1 of the SAP).

Secondary: KOOS Subscores

End point title	KOOS Subscores

End point description:

End point type	Secondary

End point timeframe:

At baseline and 6 weks, 3, 12, 18, 36, 48 and 60 months after treatment

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	24	
Units: 0-100	24	25	24	

Attachments (see zip file)	Table of KOOS subscores/Tables_KOOS_subscores.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: MOCART

End point title	MOCART

End point description:

End point type	Secondary

End point timeframe:

after 3, 12, 18, 24, 36, 48 and 60 months

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	19	
Units: 0-100	20	19	19	

Attachments (see zip file)	MOCART Scores Table/MOCART_table.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Bern Score

End point title	Bern Score

End point description:

End point type	Secondary

End point timeframe:

at 12 months

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	1	1	
Units: 0-9	5	1	1	

Attachments (see zip file)	Bern Scores Table/Bern_Table.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: modified Lysholm score

End point title	modified Lysholm score

End point description:

End point type	Secondary

End point timeframe:

at baseline and at all time points: 6 weeks, 3, 6, 12 months (final assessment) and follow-up: 18, 24, 36, 48, 60 months after transplantation

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	24	
Units: 0-24	24	25	24	

Attachments (see zip file)	modified Lysholm Table/Lysholm_Table.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from baseline to 60 months follow up

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Group A

Reporting group description:

Low-dose group receiving 3-7 spheroids per square cm defect size: Safety analyses and assessments were conducted with all patients treated (safety population, with N = 25 in each of the three treatment groups. According to the study protocol, each patient was to receive a single dose of chondrosphere. In fact two patients did not receive any chondrosphere, but did undergo arthroscopy; the latter was a study-specific procedure and these two patients are therefore included in the safety population and in all safety analyses except where a statement to the contrary is made.

Reporting group title	Group B

Reporting group description:

Low-dose group receiving 10-30 spheroids per square cm defect size: Safety analyses and assessments were conducted with all patients treated (safety population, with N = 25 in each of the three treatment groups. According to the study protocol, each patient was to receive a single dose of chondrosphere. In fact two patients did not receive any chondrosphere, but did undergo arthroscopy; the latter was a study-specific procedure and these two patients are therefore included in the safety population and in all safety analyses except where a statement to the contrary is made.

Reporting group title	Group C

Reporting group description:

Low-dose group receiving 40-70 spheroids per square cm defect size: Safety analyses and assessments were conducted with all patients treated (safety population, with N = 25 in each of the three treatment groups. According to the study protocol, each patient was to receive a single dose of chondrosphere. In fact two patients did not receive any chondrosphere, but did undergo arthroscopy; the latter was a study-specific procedure and these two patients are therefore included in the safety population and in all safety analyses except where a statement to the contrary is made.

Serious adverse events	Group A	Group B	Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)	5 / 25 (20.00%)	8 / 25 (32.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Meniscus injury			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic nerve injury			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
alternative dictionary used: MedDRA 21			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cartilage graft			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal prolapse			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
alternative dictionary used: MedDRA 21			

subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine cyst			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chondropathy			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondromalacia			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cartilage hypertrophy			
alternative dictionary used: MedDRA 21			

subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondrocalcinosis			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extraskeletal ossification			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Group A	Group B	Group C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 25 (88.00%)	24 / 25 (96.00%)	23 / 25 (92.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Soft tissue neoplasm			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Deep vein thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Skin neoplasm excision			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Tooth extraction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	1	2	0

Adverse drug reaction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tenderness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
House dust allergy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Sarcoidosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinitis seasonal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tonsillar inflammation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 25 (8.00%)	3 / 25 (12.00%)	6 / 25 (24.00%)
occurrences (all)	2	3	7
Fall			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Meniscus injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Contusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hand fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Ligament rupture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Post concussion syndrome			

subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Scar			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Upper limb fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Wound dehiscence			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	14	0	38
Aphasia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hyperaesthesia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Sciatica			

subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Bone marrow oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Inner ear inflammation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Sudden hearing loss			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal tract irritation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vomiting			

subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Scar pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	17 / 25 (68.00%)	22 / 25 (88.00%)	20 / 25 (80.00%)
occurrences (all)	19	27	27
Arthralgia			
subjects affected / exposed	5 / 25 (20.00%)	7 / 25 (28.00%)	9 / 25 (36.00%)
occurrences (all)	11	8	12
Joint swelling			
subjects affected / exposed	5 / 25 (20.00%)	5 / 25 (20.00%)	1 / 25 (4.00%)
occurrences (all)	6	5	2
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	3 / 25 (12.00%)
occurrences (all)	2	1	3
Joint noise			
subjects affected / exposed	0 / 25 (0.00%)	4 / 25 (16.00%)	2 / 25 (8.00%)
occurrences (all)	0	4	2
Tendonitis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	2	1	2

Intervertebral disc protrusion			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Joint lock			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Osteoarthritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Bone cyst			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Ligament disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Muscle atrophy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Sacroiliitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 25 (12.00%)	6 / 25 (24.00%)	2 / 25 (8.00%)
occurrences (all)	3	7	7
Tonsillitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Borrelia infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tooth infection			

subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Hyperthyroidism			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
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

None reported