Clinical trial results:
A prospective multi-centre, randomised, controlled study to evaluate the safety and preliminary effectiveness of NVD-001 for the treatment of low grade degenerative lumbar spondylolisthesis by interbody fusion (L1 – S1).

Summary

EudraCT number	2016-002642-23
Trial protocol	BE PL CZ
Global end of trial date	09 December 2020

Results information

Result version number	v1 (current)
This version publication date	01 July 2022
First version publication date	01 July 2022

Trial information

Trial identification

Sponsor protocol code	NVD-CLN01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03100032
WHO universal trial number (UTN)	-
Other trial identifiers	UMIN: UMIN000026062

Notes:

Sponsors

Sponsor organisation name	Novadip Biosciences
Sponsor organisation address	Watson & Crick Hill, Rue Granbonpré 11, Mont-saint Guibert, Belgium, 1435
Public contact	Regulatory Affairs Manager, Novadip Biosciences, Helene.servais@novadip.com
Scientific contact	Clinical & Medical Manager, Novadip Biosciences, Dieter.frijns@novadip.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	01 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2020
Global end of trial reached?	Yes
Global end of trial date	09 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety (local and systemic) of a specific surgical intervention with the use of NVD-001 (AEs, AESI, SAEs) in patients with symptomatic low-grade degenerative spondylolisthesis grade I or II undergoing surgery for spinal fusion of one vertebral segment (L1-S1).

Protection of trial subjects:

Postoperatively, the patients underwent 5 FU visits to assess safety (AEs, AEs of special interest [AESI], SAEs), surgical characteristics (blood loss, duration of hospital stay)
Additional product specific safety measures were performed:
1. Safety lab testing
2. Scan of implant region and Chest.
-Signs of local toxicity of experimental product have been evaluated on CT and radiographic images by the local radiologist and the principal investigator as well as by the independent radiologist(s) and include:

Trabecular bone resorption
Intravertebral cystic changes
Soft tissue calcification/ossification
Peridiscal soft tissue swelling
Hyperostosis
Tumour growth

-Signs of systemic toxicity have been evaluated on chest radiographs by the local radiologist and include appearance of calcification/ ossification on serial X-Rays in comparison with preoperative X-Rays.

Ectopic bone formation

Background therapy:

Subjects in the control group will be treated with autologous cancellous bone harvested at the time of the spinal fusion surgery. As harvesting bone from the iliac crest is associated with a series of complications and morbidity, only bone chips collected during laminectomy are allowed. If insufficient volume is available to fill and surround the cage(s), DBM can be added (as per hospital protocol). The trade name and manufacturer name of the product as well as the volume used will be recorded in the eCRF.

NOTE: patient numbers:
23 NVD-001
9 comparator SOC

Age range: --> the system did not allow to complete the below data correctly in age breakdown
18-64: 25
>64: 8

Evidence for comparator: -

Actual start date of recruitment	01 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czechia: 7
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 48 patients were screened by 7 principal investigators (7 centers) from 3 countries (Belgium, Czech Republic and Poland) between 01 February 2017 and 31 July 2018.Therefore, a total of 32 patients were included (01 February 2017 to 29 June 2018), randomized and treated either with NVD-001 (N=23; 71.9%) or SOC (N=9; 28.1%).

Pre-assignment

Screening details:

A total of 48 patients were screened by 7 principal investigators (7 centers) from 3 countries (Belgium, Czech Republic and Poland) between 01 February 2017 and 31 July 2018 . Eleven patients were considered as screen failures. Five patients dropped out from the study before surgery.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of Care (SOC)

Arm description:

Subjects of the control group will be treated with autologous cancellous bone locally harvested during the same operation.
At the Investigator’s discretion, one or two interbody PEEK cage(s) is/are to be filled with and surrounded by autologous locally harvested cancellous bone (laminectomy) before implantation.
As harvesting bone from the iliac crest is associated with a series of complications and morbidity, only bone chips (spinous process/lamina) collected during laminectomy are allowed. If insufficient volume is available to fill and surround the cage(s), DBM can be added (as per hospital protocol). The trade name of the product and volume used will be recorded in the eCRF.

Arm type	Active comparator
Investigational medicinal product name	Autologous bone
Investigational medicinal product code	Autologous bone harvested from the patient
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

Subjects of the control group will be treated with autologous cancellous bone harvested locally. One or two interbody PEEK cage(s) is/are to be filled and surrounded with autologous locally harvested cancellous bone (laminectomy). As harvesting bone from the iliac crest is associated with a series of complications and morbidity, only bone chips (spinous process/lamina) collected during laminectomy are allowed.

In the SOC group, the quantity of harvested bone chips was 3.4 ± 1.9 cc. Harvesting of bone chips was laminae in 8 patients (88.9%) and spinous in 1 patient (11.1%) of the SOC group. DBM was used in one patient only (11.1%).

Arm title	NVD-001

Arm description:

The investigational Advanced Therapy Medicinal Product NVD 001 is an autologous cellular therapy. The product is obtained after isolation of ASCs from a fat tissue sample obtained by a minimally invasive subcutaneous procedure (liposuction) in the abdominal region of the patient, and their differentiation in osteogenic cells with a proprietary quality controlled DBM into a 3D-bone implant. NVD 001 is characterized in view to obtain the same properties as a real bone, non-immunogenic, with a desirable handling and mechanical characteristics. In the current study, NVD 001 must be used exclusively in conjunction with an interbody somatic cage and bilateral pedicle screw fixation with connecting rods.

Arm type	Experimental
Investigational medicinal product name	NVD-001
Investigational medicinal product code	NVD-001
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

It is expected that 3 containers with NVD 001 will be available per patient for the surgical intervention. Information on IMP including the total volume IMP sent (in grams) and the total volume of unused IMP (in grams) was variable and has been provided before the implant surgery to the sites by the sponsor. This information will also provide an estimated volume of used IMP (in grams).

In the NVD-001 group, the quantity of IMP sent on site was 19.6 ± 2.3 g, the quantity used was 5.7 ± 3.6 g and the quantity unused was 13.9 ± 3.4 g

Number of subjects in period 1	Standard of Care (SOC)	NVD-001
Started	9	23
Completed	9	23

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Safety will be assessed by:
- Collecting all adverse events for incidence, severity, relatedness, required action and outcome, up to 12 months post-surgery.
- Collecting all SAEs up to 24 months post-surgery.
- Collecting AESI up to 24 months post-surgery as part of local and systemic toxicity such as:

Signs of local toxicity of experimental product will be evaluated on CT and radiographic images by the local radiologist and the principal investigator as well as by the independent radiologist(s) and include:
Trabecular bone resorption
Intravertebral cystic changes
Soft tissue calcification/ossification
Peridiscal soft tissue swelling
Hyperostosis
Tumour growth

Signs of systemic toxicity will be evaluated on chest radiographs by the local radiologist and include appearance of calcification/ ossification on serial X-Rays in comparison with preoperative X-Rays.
Ectopic bone formation

Reporting group values	Overall trial	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
18+	32	32	
Age continuous Units: years			
arithmetic mean	55.2		
standard deviation	± 11.4	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	13	13	
BMI Units: kg/m2			
arithmetic mean	27.3		
standard deviation	± 4.4	-	

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A modified Intent-to-Treat (mITT) cohort consisting of all subjects having been included, randomized, treated with NVD-001 or Standard of Care (SOC) and for whom at least one safety assessment was available after surgery.

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

A per protocol (PP) cohort consisting of all subjects from the mITT for whom no major protocol deviations had been reported. Based on the observation that for some patients the implanted volume of

NVD-001 was very low, one additional PP elimination criterion was added, that was not included into the protocol, as it was believed that patients with a NVD-001 volume/disk height ratio lower than 50% would have a significant impact in the NVD-001 efficacy outcomes and would not be representative for the bone healing capacity of NVD-001. The rationale is that the higher the residual disk height, the higher the NVD-001 volume should be to fill the residual interbody space, generating the required bone to graft contact surface.

Reporting group values	mITT	Per Protocol	
Number of subjects	32	20	
Age categorical Units: Subjects			
18+	32	20	
Age continuous Units: years			
arithmetic mean	55.2	56.7	
standard deviation	± 11.4	± 10.8	
Gender categorical Units: Subjects			
Female	19	12	
Male	13	8	
BMI Units: kg/m2			
arithmetic mean	27.3	27.3	
standard deviation	± 4.4	± 4.3	

End points

End points reporting groups

Reporting group title	Standard of Care (SOC)

Reporting group description:

Subjects of the control group will be treated with autologous cancellous bone locally harvested during the same operation.
At the Investigator's discretion, one or two interbody PEEK cage(s) is/are to be filled with and surrounded by autologous locally harvested cancellous bone (laminectomy) before implantation.
As harvesting bone from the iliac crest is associated with a series of complications and morbidity, only bone chips (spinous process/lamina) collected during laminectomy are allowed. If insufficient volume is available to fill and surround the cage(s), DBM can be added (as per hospital protocol). The trade name of the product and volume used will be recorded in the eCRF.

Reporting group title	NVD-001

Reporting group description:

The investigational Advanced Therapy Medicinal Product NVD 001 is an autologous cellular therapy. The product is obtained after isolation of ASCs from a fat tissue sample obtained by a minimally invasive subcutaneous procedure (liposuction) in the abdominal region of the patient, and their differentiation in osteogenic cells with a proprietary quality controlled DBM into a 3D-bone implant. NVD 001 is characterized in view to obtain the same properties as a real bone, non-immunogenic, with a desirable handling and mechanical characteristics. In the current study, NVD 001 must be used exclusively in conjunction with an interbody somatic cage and bilateral pedicle screw fixation with connecting rods.

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A modified Intent-to-Treat (mITT) cohort consisting of all subjects having been included, randomized, treated with NVD-001 or Standard of Care (SOC) and for whom at least one safety assessment was available after surgery.

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

A per protocol (PP) cohort consisting of all subjects from the mITT for whom no major protocol deviations had been reported. Based on the observation that for some patients the implanted volume of NVD-001 was very low, one additional PP elimination criterion was added, that was not included into the protocol, as it was believed that patients with a NVD-001 volume/disk height ratio lower than 50% would have a significant impact in the NVD-001 efficacy outcomes and would not be representative for the bone healing capacity of NVD-001. The rationale is that the higher the residual disk height, the higher the NVD-001 volume should be to fill the residual interbody space, generating the required bone to graft contact surface.

Primary: Safety

End point title	Safety

End point description:

All adverse events for incidence, severity, relatedness, required action and outcome, up to 12 months post-surgery.
All SAEs up to 24 months post-surgery.
All AESI up to 24 months post-surgery as part of local and systemic toxicity such as signs of local toxicity of experimental product will be evaluated on CT and radiographic images by the local radiologist and the principal investigator as well as by the independent radiologist(s) and include:

- Trabecular bone resorption
- Intravertebral cystic changes
- Soft tissue calcification/ossification
- Peridiscal soft tissue swelling
- Hyperostosis
- Tumour growth

Signs of systemic toxicity will be evaluated on chest radiographs by the local radiologist and include appearance of calcification/ ossification on serial X-Rays in comparison with preoperative X-Rays.

- Ectopic bone formation

End point type	Primary

End point timeframe:

D0 till 24m post-grafting

End point values	Standard of Care (SOC)	NVD-001	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9[1]	23[2]	32[3]	
Units: AE				
Treatment Emergent AE (TAE)	22	55	77	
Mild TAE	17	40	57	
Moderate TAE	5	12	17	
Severe TAE	0	3	3	
SAE	1	5	6	
Surgical procedure related TAE	13	28	41	
Bone Graft Related TAE	0	0	0	
AE of Special Interest (AESI)	0	2	2	

Notes:

[1] - SOC

[2] - NVD-001

[3] - All mITT patients

Statistical analyses

Statistical analysis title	Fisher’s exact tests

Statistical analysis description:

The frequency of treatment-emergent AEs through Month 12 (for all types of AEs) and Month 24 (AESI, SAEs) will be summarised by treatment group. Treatment-emergent AEs are those AEs that started or were present but worsened after completion of surgery.

Comparison groups	NVD-001 v Standard of Care (SOC)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0
Method	Fisher exact

Notes:

[4] - this is only descriptive without statistics

Secondary: Average Pain (Brief pain Inventory questionnaire)

End point title	Average Pain (Brief pain Inventory questionnaire)

End point description:

The BPI-SF is a short, self-report or interview questionnaire, designed to assess the severity of pain and the impact of pain on daily functions. Four pain severity items (worst pain, least pain, average pain, and pain now) and seven pain interference items measuring the level of interference with a given function caused by pain (general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life) are rated on 0–10 scales.

This endpoint focusses on average pain.

End point type	Secondary

End point timeframe:

D0-M24

End point values	Standard of Care (SOC)	NVD-001	Per Protocol	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	9	23	20	
Units: VAS Score				
arithmetic mean (standard deviation)				
V0	5.2 (± 2.775)	4.07 (± 2.631)	1.67 (± 1.155)	
V6 (12m)	1.8 (± 1.304)	2.27 (± 2.374)	1.92 (± 2.397)	
V8 (24m)	1.67 (± 1.155)	1.92 (± 2.397)	1.87 (± 2.187)	

Statistical analyses

No statistical analyses for this end point

Secondary: Trabecular bone bridging score

End point title	Trabecular bone bridging score

End point description:

End point type	Secondary

End point timeframe:

6m and 24m post grafting surgery

End point values	Standard of Care (SOC)	NVD-001	mITT	Per Protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	9[5]	23[6]	22[7]	15
Units: % bridging				
6m - 0%	0	14	14	9
6m - 1-25%	1	4	4	4
6m - 26-50%	1	0	0	0
6m - 51-75%	4	0	0	2
6m - 76-99%	3	5	5	5
6m - 100%	0	0	0	0
12m - 0%	0	11	11	7
12m - 1-25%	0	2	2	1
12m - 26-50%	0	2	2	1
12m 51-75%	1	2	1	1
12m - 76-99%	7	12	5	8
12m - 100%	1	2	1	1

Notes:

[5] - 6m or 12m FU CT mITT

[6] - 6m or 12m FU CT NVD-001 mITT

[7] - mITT NVD001 vs PP NVD001

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening till 24 months post-Grafting Surgery

Adverse event reporting additional description:

- Collecting all adverse events for incidence, severity, relatedness, required action and outcome, up to 12 months post-surgery.
- Collecting all SAEs up to 24 months post-surgery.
- Collecting AESI up to 24 months post-surgery as part of local and systemic toxicity

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Standard of Care (SOC)

Reporting group description:

Subjects of the control group will be treated with autologous cancellous bone locally harvested during the same operation.
At the Investigator's discretion, one or two interbody PEEK cage(s) is/are to be filled with and surrounded by autologous locally harvested cancellous bone (laminectomy) before implantation.

Reporting group title	NVD-001

Reporting group description:

The investigational Advanced Therapy Medicinal Product NVD 001 is an autologous cellular therapy. The product is obtained after isolation of ASCs from a fat tissue sample obtained by a minimally invasive subcutaneous procedure (liposuction) in the abdominal region of the patient, and their differentiation in osteogenic cells with a proprietary quality controlled DBM into a 3D-bone implant. NVD 001 is characterized in view to obtain the same properties as a real bone, non-immunogenic, with a desirable handling and mechanical characteristics. In the current study, NVD 001 must be used exclusively in conjunction with an interbody somatic cage and bilateral pedicle screw fixation with connecting rods.

Serious adverse events	Standard of Care (SOC)	NVD-001	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	3 / 23 (13.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Incisional hernia			

subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard of Care (SOC)	NVD-001	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	10 / 23 (43.48%)	
Investigations			
Pseudomonas test positive			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Blood potassium increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Blood pressure increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	2 / 9 (22.22%)	5 / 23 (21.74%)	
occurrences (all)	2	5	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Red blood cell count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Red blood cell sedimentation rate increased			
subjects affected / exposed	2 / 9 (22.22%)	4 / 23 (17.39%)	
occurrences (all)	2	4	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 9 (11.11%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dural Tear			

subjects affected / exposed	0 / 9 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Post procedural haematoma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	1 / 9 (11.11%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Radicular pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	1 / 9 (11.11%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Food poisoning			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Gastric ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 9 (22.22%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Bone hypertrophy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Osteolysis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Impaired fasting glucose			
subjects affected / exposed	2 / 9 (22.22%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	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