Clinical trial results:
Patient and evaluator blinded non-inferiority study on safety, tolerability and lumbar fusion efficacy of a single administration of Osteogrow (rhBMP6 in autologous blood coagulum (ABC) carrier) in adult patients treated by posterolateral lumbar interbody fusion (PLIF) for degenerative disc disease

Summary

EudraCT number	2017-000860-14
Trial protocol	AT
Global end of trial date	13 March 2023

Results information

Result version number	v1 (current)
This version publication date	11 February 2026
First version publication date	11 February 2026

Trial information

Trial identification

Sponsor protocol code	GR-OG-279239-03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Genera Research Ltd
Sponsor organisation address	Svetonedjeljska 2, Kalinovica, Croatia, 10436 Rakov Potok
Public contact	Slobodan Vukicevic, Genera Research Ltd, +385 (0)16474229, info@genera-research.com
Scientific contact	Slobodan Vukicevic, Genera Research Ltd, +385 (0)16474229, info@genera-research.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	19 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2023
Global end of trial reached?	Yes
Global end of trial date	13 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate safety and composite endpoint non-inferiority of one of the two doses of Osteogrow+Allograft delivered bilaterally between transverse processes of a single lumbar spine segment in comparison to autologous iliac crest bone graft (with a non-inferiority absolute margin of 10% as patient success at 20 months after surgery)

Protection of trial subjects:

Patients were enrolled in three stages, separated by at least 3 months follow-up of patients included in the preceding stage, an interim review of the collected safety data by the Independent Data and Safety Monitoring Board (IDSMB), and a "go/no-go" decision for progression into the next stage based on the IDSMB recommendation. As an additional precaution, the first stage was conducted at a single clinical site.
All patients were screened within one month before surgery, operated in a hospital setting and kept in the hospital for at least 10 days (Stage 1 only), or for 5 to 13 days after surgery, depending on the postoperative course. Follow-up visits were performed on the day of hospital discharge and 3 weeks, 6 weeks and 3, 6, 12 and 20 months after surgery. Each visit entailed various clinical assessments, laboratory tests, radiological procedures and/or questionnaires.

Background therapy:

PLIF procedure entails lumbar interbody fusion by means of intervertebral cages filled with local (host) bone, and posterior stabilization of the treated spinal segment with pedicle screws.

Evidence for comparator:

Autologous bone graft from the iliac crest is considered the gold standard for stimulation of bone formation.

Actual start date of recruitment	25 May 2018
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	Austria: 143
Worldwide total number of subjects	143
EEA total number of subjects	143

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	106
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at three centers in Austria, from 26 May 2018 (FPFV) until 13 March 2023 (LPLV)

Pre-assignment

Screening details:

Patients with symptomatic L3-S1 DDD were screened within one month before surgery by medical history, physical exam, clinical laboratory tests, urine drug screen, urine pregnancy test (if applicable), and ECG. Imaging (X-rays, MRI/CT) depended on the availability of recent images. Other procedures were related to the collection of baseline data.

Pre-assignment period milestones

Number of subjects started	162[1]
Number of subjects completed	143

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 14
Reason: Number of subjects	Surgery cancelled: 3
Reason: Number of subjects	Physician decision: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 162 subjects were assessed for eligibility. Only subjects who were eligible and randomized (N=143) were considered enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Assessor, Investigator

Blinding implementation details:

All patients were blinded to treatment allocation. Investigators who operated on patients were unblinded. Those who performed postoperative physical and neurological examinations were blinded and called blinded evaluators. They were to evaluate adverse events as well, but this could not be confirmed in all cases. Other blinded evaluations included all radiographic measurements or assessments and anti-rhBMP6 antibody tests, which were performed centrally by blinded personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of Care

Arm description:

360 degrees stabilization with intervertebral cages filled with local (host) bone, instrumentation with pedicle screws, and bilateral autologous bone graft from iliac crest in the lateral gutter (approximately 5 cc per side).

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Arm title	HD OSTEOGROW

Arm description:

Standard of Care but with Osteogrow (1 mg rhBMP6 in 5 mL ABC; 0.2 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 2 mg rhBMP6 in total

Arm type	Experimental

Investigational medicinal product name	rhBMP6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for implantation paste
Routes of administration	Implantation

Dosage and administration details:

Osteogrow implants were prepared in the operating room using Osteogrow kit (2 mg rhBMP6 in vials, solvent and ancillary items), allograft, and 10 mL of patient's peripheral blood drawn approximately 60 min before the anticipated time implantation. Osteogrow was implanted into the left and right lateral gutter, one implant per side, after stabilization of the treated spinal level with intervertebral cages filled with local (host) bone and pedicle screws.

Arm title	LD OSTEOGROW

Arm description:

Standard of Care but with Osteogrow (0.5 mg rhBMP6 in 5 mL ABC; 0.1 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 1 mg rhBMP6 in total

Arm type	Experimental
Investigational medicinal product name	rhBMP6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for implantation paste
Routes of administration	Implantation

Dosage and administration details:

Osteogrow implants were prepared in the operating room using Osteogrow kit (1 mg rhBMP6 in vials, solvent and ancillary items), allograft, and 10 mL of patient's peripheral blood drawn approximately 60 min before the anticipated time implantation. Osteogrow was implanted into the left and right lateral gutter, one implant per side, after stabilization of the treated spinal level with intervertebral cages filled with local (host) bone and pedicle screws.

Number of subjects in period 1	Standard of Care	HD OSTEOGROW	LD OSTEOGROW
Started	62	61	20
Completed	51	52	18
Not completed	11	9	2
Adverse event, serious fatal	3	-	-
Consent withdrawn by subject	2	7	2
Adverse event, non-fatal	2	-	-
Lost to follow-up	4	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Standard of Care
Reporting group description:	
360 degrees stabilization with intervertebral cages filled with local (host) bone, instrumentation with pedicle screws, and bilateral autologous bone graft from iliac crest in the lateral gutter (approximately 5 cc per side).	
Reporting group title	HD OSTEOGROW
Reporting group description:	
Standard of Care but with Osteogrow (1 mg rhBMP6 in 5 mL ABC; 0.2 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 2 mg rhBMP6 in total	
Reporting group title	LD OSTEOGROW
Reporting group description:	
Standard of Care but with Osteogrow (0.5 mg rhBMP6 in 5 mL ABC; 0.1 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 1 mg rhBMP6 in total	

Reporting group values	Standard of Care	HD OSTEOGROW	LD OSTEOGROW
Number of subjects	62	61	20
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)	43	49	15
From 65-84 years	19	12	5
85 years and over	0	0	0
Adults (18-64)	0	0	0
Adults	0	0	0
Age continuous Units: years			
arithmetic mean	57.8	54.5	56.2
standard deviation	± 11.7	± 12.2	± 13.3
Gender categorical Units: Subjects			
Female	33	32	10
Male	29	29	10

Reporting group values	Total		
Number of subjects	143		
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)	107		
From 65-84 years	36		
85 years and over	0		
Adults (18-64)	0		
Adults	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	75		
Male	68		

Subject analysis sets

Subject analysis set title	Standard of Care (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received study treatment, were followed-up for at least 6 months, and had baseline data needed to determine the primary endpoint	
Subject analysis set title	HD Osteogrow (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received study treatment, were followed-up for at least 6 months, and had baseline data needed to determine the primary endpoint	
Subject analysis set title	LD Osteogrow (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received study treatment, were followed-up for at least 6 months, and had baseline data needed to determine the primary endpoint	
Subject analysis set title	Standard of Care (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received study treatment	
Subject analysis set title	HD Osteogrow (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received study treatment	
Subject analysis set title	LD Osteogrow (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received study treatment	

Reporting group values	Standard of Care (mITT)	HD Osteogrow (mITT)	LD Osteogrow (mITT)
Number of subjects	55	56	19
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	38	46	14
From 65-84 years	17	10	5
85 years and over			
Adults (18-64)			
Adults			
Age continuous			
Units: years			
arithmetic mean	57.8	54.6	54.9
standard deviation	± 11.7	± 11.3	± 12.4
Gender categorical			
Units: Subjects			
Female	29	31	10
Male	26	25	9

Reporting group values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)
Number of subjects	61	61	20
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	42	49	15
From 65-84 years	19	12	5
85 years and over			
Adults (18-64)			
Adults			
Age continuous			
Units: years			
arithmetic mean	57.9	54.5	56.2
standard deviation	± 11.9	± 12.2	± 13.3
Gender categorical			
Units: Subjects			
Female	32	32	10
Male	29	29	10

End points

End points reporting groups

Reporting group title	Standard of Care
Reporting group description:	
360 degrees stabilization with intervertebral cages filled with local (host) bone, instrumentation with pedicle screws, and bilateral autologous bone graft from iliac crest in the lateral gutter (approximately 5 cc per side).	
Reporting group title	HD OSTEOGROW
Reporting group description:	
Standard of Care but with Osteogrow (1 mg rhBMP6 in 5 mL ABC; 0.2 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 2 mg rhBMP6 in total	
Reporting group title	LD OSTEOGROW
Reporting group description:	
Standard of Care but with Osteogrow (0.5 mg rhBMP6 in 5 mL ABC; 0.1 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 1 mg rhBMP6 in total	
Subject analysis set title	Standard of Care (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received study treatment, were followed-up for at least 6 months, and had baseline data needed to determine the primary endpoint	
Subject analysis set title	HD Osteogrow (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received study treatment, were followed-up for at least 6 months, and had baseline data needed to determine the primary endpoint	
Subject analysis set title	LD Osteogrow (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received study treatment, were followed-up for at least 6 months, and had baseline data needed to determine the primary endpoint	
Subject analysis set title	Standard of Care (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received study treatment	
Subject analysis set title	HD Osteogrow (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received study treatment	
Subject analysis set title	LD Osteogrow (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received study treatment	

Primary: Overall clinical success (OCS) 20 months after surgery

End point title	Overall clinical success (OCS) 20 months after surgery
End point description:	
OCS was defined as all of the following: (a) radiographic fusion (no evidence of intervertebral motion with bilateral bony bridging); (b) spinal function improvement (decrease in ODI by ≥15 points); (c) maintenance or improvement in neurological status (equals to neurological success; derived from 11 components); (d) no additional surgical procedures related to the treated spinal level; and (e) no serious implant- or implant/surgical procedure-associated adverse events.	

To preserve the power of the trial, all comparisons were limited to the main arms (SoC and HD Osteogrow) where missing data on individual components of the OCS were imputed using multiple imputation by chained equations (MICE) or univariate methods as described in the applicable secondary endpoints, and success rates were derived from 20 imputed datasets. No OCS was observed in the LD Osteogrow arm.

End point type	Primary

End point timeframe:

Month 20 after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)	1.9	0.2		

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: OCS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and the results were pooled according to Rubin's rules. Non-inferiority/superiority (NI/S) was assessed based on the covariate-unadjusted 1-sided 95% CI for the HD Osteogrow - SoC difference in pooled percentages, calculated using Wald's z statistic for a pair of proportions with non-pooled standard errors.

Comparison groups	HD Osteogrow (mITT) v Standard of Care (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	-1.7
Confidence interval	
level	95 %
sides	1-sided
lower limit	-5.2

Notes:

[1] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Secondary: Overall clinical success (OCS) at 6 and 12 months after surgery

End point title	Overall clinical success (OCS) at 6 and 12 months after surgery

End point description:

Please refer to the description of the primary endpoint (OCS 20 months after surgery).
In accordance with the planned sequential non-inferiority/superiority (NI/S) testing of HD Osteogrow vs. SoC (NI at month 20 > S at month 20 > S at month 12 > S at month 6), stopping after the first non-rejection of the null hypothesis and leaving the remaining hypotheses non-rejected, the superiority of HD Osteogrow vs. SoC at 12 and 6 months was not tested. No OCS was observed in the LD Osteogrow arm at any time point.

End point type	Secondary

End point timeframe:

6 and 12 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)				
Month 6	0.0	1.8		
Month 12	2.0	3.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic fusion (RF) at 6, 12 and 20 months after surgery

End point title	Radiographic fusion (RF) at 6, 12 and 20 months after surgery

End point description:

RF was defined as no evidence of intervertebral motion at the treated spinal level (≤3 mm translation and <5 degrees angular motion on lateral flexion/extension x-rays) with radiographic evidence of bridging trabecular bone (continuous bony connection from the superior to inferior transverse process) on both sides. The latter was assessed by consensus of 3 blinded assessors based on CT scans or lumbar spine x-rays, if a CT scan was not available.
All comparisons were limited to the main arms (SoC and HD Osteogrow) where missing data on motion and bridging at 6, 12 and 20 months were imputed using multiple imputation by chained equations (MICE) as described in endpoints "no evidence of motion" and "bony bridging". RF rates shown below were pooled from 20 imputed datasets. No RF was observed in the LD Osteogrow arm.

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)				
Month 6	3.8	5.6		
Month 12	4.4	6.0		
Month 20	6.2	4.2		

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: RF at month 20

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and the results were pooled according to Rubin's rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for the primary endpoint, but with a fixed testing sequence (NI at month 20 > S at month 20 > S at month 12 > S at month 6) stopping after the first non-rejection of the null hypothesis and leaving the remaining hypotheses non-rejected.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	-2
Confidence interval	
level	95 %
sides	1-sided
lower limit	-9.5

Notes:

[2] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Secondary: The size of the bone generated between the transverse processes (minimum axial diameter of the bridges)

End point title	The size of the bone generated between the transverse processes (minimum axial diameter of the bridges)

End point description:

For each observed bony bridge, the minimum axial diameter (MAD) of the bridge was measured by three blinded assessors, and the three measurements were averaged.
The collected data were summarized for all bridges observed in the mITT dataset and analysed descriptively. In the LD Osteogrow arm, two bridges were observed at month 12 (MAD 6.3 mm for both) and one at month 6 (MAD 4.3 mm).

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[3]	8[4]		
Units: Millimeter				
arithmetic mean (standard deviation)				
Month 6	4.1 (± 2.4)	3.6 (± 1.6)		
Month 12	4.9 (± 1.9)	5.2 (± 2.6)		
Month 20	5.0 (± 2.3)	4.8 (± 3.0)		

Notes:

[3] - The total number of bridges in the mITT dataset (19 in month 20, 18 in month 12, and 17 in month 6)
[4] - The total number of bridges in the mITT dataset (8 in month 20, 9 in month 12, and 11 in month 6)

Statistical analyses

No statistical analyses for this end point

Secondary: Oswestry Disability Index (ODI) over time

End point title	Oswestry Disability Index (ODI) over time

End point description:

ODI (range 0 to 100) is a measure of functional impairment/disability related to lumbar spine problems, derived from the patient's responses to the ODI questionnaire. Higher ODI values indicate greater disability.
Comparisons were limited to the main arms (SoC and HD Osteogrow) where missing ODI values were imputed by visit using multiple imputation by chained equations (MICE); the predictive mean matching was employed with 5 donor values and the following predictor variables: treatment arm, baseline ODI, "no evidence of motion", SF36 PCS score, ODI Pain score, age, smoking, body mass index, and sex. The mean covariate-adjusted scores pooled from 20 imputed datasets are shown below. Unadjusted mean scores for all arms, based on actual observations only, are shown in the attachment.

End point type	Secondary

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Score points				
least squares mean (standard error)				
Week 3	46.1 (± 2.19)	45.6 (± 2.16)		
Week 6	38.1 (± 2.38)	38.1 (± 2.26)		
Month 3	33.3 (± 2.41)	32.4 (± 2.39)		
Month 6	31.0 (± 2.43)	29.1 (± 2.37)		
Month 12	30.9 (± 2.98)	26.6 (± 2.88)		
Month 20	35.3 (± 2.84)	25.6 (± 2.73)		

Attachments (see zip file)	Longitudinal analysis of ODI scores/Figure 14.3.8.2.pdf

Statistical analyses

Statistical analysis title	ODI over time (main arms): Month 20

Statistical analysis description:

Mean ODI values over time were modeled for each of the 20 imputed datasets using GLS-fitted MMRM, a fixed-effect general linear model for repeated measurements with Kenward-Roger adjustment for degrees of freedom, REML estimation of the (co)variance parameters, unstructured covariance pattern, and adjustment for age and baseline value (both interacting with visit). The obtained estimates were pooled and compared between arms at each visit using Wald's t statistic; 2-sided tests at α=0.05.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0437 [6]
Method	GLS-fitted MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-9.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.21
upper limit	-0.216
Variability estimate	Standard error of the mean
Dispersion value	4.01

Notes:

[5] - Wald’s t statistic (Kenward-Roger scaled Wald’s statistic) is adjusted through both the denominator degrees of freedom and appropriate inflation of the variance-covariance matrix, accounting for small sample sizes and mild deviations from normality of the normalized model residuals. P-values and 95% CIs for mean (pooled) HD Osteogrow-SoC differences were both unadjusted and adjusted for multiplicity using the mvt method. Results for earlier time points are shown in the attachment.
[6] - Wald’s t statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at 6, 12 and 20 months as they were most relevant from a clinical perspective).

Secondary: Spinal function (ODI) success at 6, 12 and 20 months after surgery

End point title	Spinal function (ODI) success at 6, 12 and 20 months after surgery

End point description:

Spinal function success (SFS), also called ODI success, was an indicator of relevant improvement in spinal function in individual subjects and was defined as a clinically meaningful reduction in ODI of ≥15 points from baseline.
All comparisons were limited to the main arms (SoC and HD Osteogrow) where missing ODI values were imputed as described for ODI over time. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in all arms, based on the total number of actual observations and interpreted as observed probabilities, are shown in the attachment.

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)				
Month 6	50.8	58.9		
Month 12	57.1	61.7		
Month 20	49.2	62.4		

Attachments (see zip file)	Longitudinal analysis of ODI success rates/Figure 14.3.11.1.pdf

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: SFS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and the results were pooled according to Rubin's rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	13.2
Confidence interval	
level	95 %
sides	1-sided
lower limit	-3

Notes:

[7] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	Age-adjusted SFS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of SFS over time were modeled for each of the 20 imputed datasets using GEE-estimated logistic regression (unstructured covariance, age interacting with visit), pooled, and compared between arms at each visit on a probability scale (marginal means estimated on a response scale) using Wald's z statistic (asymptotic normal approximation of the distribution of the relevant test statistic under infinite degrees of freedom); 2-sided tests at α=0.05.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.287 [9]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	0.1511
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0816
upper limit	0.384
Variability estimate	Standard error of the mean
Dispersion value	0.0994

Notes:

[8] - P-values and 95% CIs for mean (pooled) HD Osteogrow-SoC differences were both unadjusted and adjusted for multiplicity using the so-called mvt method, a parametric exact method where the critical value for the test statistic is derived from the multivariate t distribution accounting for the estimated means and covariances. Results for earlier time points are shown in the attachment.
[9] - Wald's z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective).

Secondary: Back pain over time

End point title	Back pain over time

End point description:

Back pain was quantified using the ODI Pain score (range 0 to 5), the raw score for the pain question in the ODI questionnaire. Higher scores indicate greater pain.

For the main arms (SoC and HD Osteogrow), missing ODI Pain scores were imputed by visit using multiple imputation by chained equations (MICE); the predictive mean matching was employed with 5 donor values and the following predictor variables: treatment arm, baseline ODI Pain score, "no evidence of motion", any unintended ossification, surgical site swelling, age, smoking, body mass index, and sex. The mean covariate-adjusted scores derived from 20 imputed datasets are shown below. Unadjusted mean scores for all arms, based on actual observations only, are shown in the attachment.

End point type	Secondary

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Score points				
least squares mean (standard error)				
Week 3	1.93 (± 0.133)	1.87 (± 0.157)		
Week 6	1.79 (± 0.146)	1.89 (± 0.127)		
Month 3	1.76 (± 0.162)	1.69 (± 0.148)		
Month 6	1.70 (± 0.174)	1.83 (± 0.158)		
Month 12	1.98 (± 0.205)	1.70 (± 0.184)		
Month 20	2.05 (± 0.189)	1.52 (± 0.171)		

Attachments (see zip file)	Longitudinal analysis of ODI Pain scores/Figure 14.3.12.3.pdf

Statistical analyses

Statistical analysis title	Back pain scores over time (main arms): Month 20

Statistical analysis description:

This was an MMRM-based analysis, performed for each of the 20 imputed datasets using GEE estimation with a robust (sandwich) empirical estimator of unstructured covariance and adjustments for age and baseline score that were allowed to vary across visits. The obtained estimates were pooled and compared between arms at each visit using Wald's z statistic (2-sided tests at α=0.05), with and without adjustment for multiplicity using the mvt method.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.0978 [11]
Method	GEE-fitted MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.535
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.142
upper limit	0.0708
Variability estimate	Standard error of the mean
Dispersion value	0.257

Notes:

[10] - MMRM assumed treating ODI Pain scores as numerical outcomes with equidistant items and was performed to obtain easily interpretable results - mean scores and their differences. It also implied equal probability of transition from one score to the other and, therefore, required a sensitivity analysis using a method suitable for handling ordinal outcomes. Results for earlier time points are shown in the attachment.
[11] - Wald's z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at 6, 12 and 20 months as they were most relevant from a clinical perspective); unadjusted p=0.0375.

Statistical analysis title	Back pain scores (ordinal regression): Month 20

Statistical analysis description:

ODI Pain scores were also modelled in each imputed dataset using GEE-estimated ordinal logistic regression (GEE estimation with category-exchangeability structure and robust standard errors, visit and arm interactions, and with an independent adjustment for age at each visit; adjustment for baseline was not meaningful). The obtained age-adjusted estimates on the latent variable scale were pooled and compared between arms in the same way as described above for MMRM.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.0347 [13]
Method	GEE-fitted ordinal regression
Parameter estimate	Mean difference (final ranked values)
Point estimate	-0.9377
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.823
upper limit	-0.0525
Variability estimate	Standard error of the mean
Dispersion value	0.376

Notes:

[12] - A latent variable is a virtual random continuous variable underlying the ordinal response, i.e., the observed scores are considered to be a categorized manifestation of some underlying continuous response. Positive estimates on the latent variable scale reflect greater odds of higher scores (for ODI Pain score this means worse condition), while negative estimates indicate greater odds of lower scores (better condition). Results were consistent with those obtained via MMRM except for month 20.
[13] - Wald's z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at 6, 12 and 20 months as they were most relevant from a clinical perspective).

Secondary: Back pain relief success (BPRS) over time

End point title	Back pain relief success (BPRS) over time

End point description:

BPRS was an indicator of relevant reduction in back pain in individual subjects and was defined as a clinically meaningful reduction in ODI Pain score of ≥1 point from baseline.
All comparisons were limited to the main arms (SoC and HD Osteogrow) where missing ODI Pain scores were imputed as described for back pain over time. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in all arms, based on the total number of actual observations and interpreted as observed probabilities, are shown in the attachment.

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of patients				
number (not applicable)				
Month 6	69.4	58.9		
Month 12	64.5	61.6		
Month 20	61.5	72.8		

Attachments (see zip file)	Longitudinal analysis of back pain relief success/Figure

Statistical analyses

Statistical analysis title	Age-adjusted BPRS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of BPRS over time were modeled and compared between the main arms in the same manner as described for spinal function success. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2905 [14]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	0.1442
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0753
upper limit	0.364
Variability estimate	Standard error of the mean
Dispersion value	0.093

Notes:

[14] - Wald’s z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective).

Statistical analysis title	NI/S of HD Osteogrow vs SoC: BPRS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and unadjusted BPRS rates were pooled according to Rubin’s rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	non-inferiority[15]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	11.3

Confidence interval	
level	95 %
sides	1-sided
lower limit	-3.7

Notes:

[15] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Secondary: Leg pain over time

End point title	Leg pain over time

End point description:

Leg pain was quantified using the LLQ Pain score (range 0 to 100), the score for the pain domain of the American Academy of Orthopedic Surgeons Lower Limb Questionnaire (LLQ questions 3 to 5). Higher scores indicate less pain.
For the main arms (SoC and HD Osteogrow), missing LLQ Pain scores were imputed by visit using multiple imputation by chained equations (MICE); the predictive mean matching was employed with 5 donor values and the following predictor variables: treatment arm, baseline LLQ Pain score, any unintended ossification, "no evidence of motion", neurological success, age, smoking, body mass index, and sex. The mean covariate-adjusted scores derived from 20 imputed datasets are shown below. Unadjusted mean scores for all arms, based on actual observations only, are shown in the attachment.

End point type	Secondary

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Score points				
least squares mean (standard error)				
Week 3	64.0 (± 2.90)	65.7 (± 2.84)		
Week 6	71.4 (± 2.79)	71.5 (± 2.87)		
Month 3	72.0 (± 2.79)	72.7 (± 2.76)		
Month 6	65.8 (± 3.02)	70.5 (± 2.96)		
Month 12	63.0 (± 3.63)	73.1 (± 3.58)		
Month 20	62.6 (± 3.16)	80.2 (± 3.06)		

Attachments (see zip file)	Longitudinal analysis of LLQ Pain scores/Figure 14.3.16.2.pdf

Statistical analyses

Statistical analysis title	Leg pain scores over time (main arms): Month 20

Statistical analysis description:

LLQ Pain scores were modelled and compared between the main arms in the same manner as described for ODI over time.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0003 [17]
Method	GLS-fitted MMRM
Parameter estimate	Mean difference (final values)
Point estimate	17.609
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.195
upper limit	28.02
Variability estimate	Standard error of the mean
Dispersion value	4.3756

Notes:

[16] - Results for earlier time points are shown in the attachment.

[17] - Wald's t statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at 6, 12 and 20 months as they were most relevant from a clinical perspective).

Secondary: Leg pain relief success (LPRS) over time

End point title	Leg pain relief success (LPRS) over time

End point description:

LPRS was an indicator of relevant reduction in leg pain in individual subjects and was defined as a clinically meaningful increase in LLQ Pain score of ≥15 points from baseline.
All comparisons were limited to the main arms (SoC and HD Osteogrow) where missing LLQ Pain scores were imputed as described for leg pain over time. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in all arms, based on the total number of actual observations and interpreted as observed probabilities, are shown in the attachment.

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of patients				
number (not applicable)				
Month 6	54.4	56.5		
Month 12	49.1	56.2		
Month 20	46.2	77.4		

Attachments (see zip file)	Longitudinal analysis of leg pain relief success/Figure

Statistical analyses

Statistical analysis title	Age-adjusted LPRS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of LPRS over time were modeled and compared between the main arms in the same manner as described for spinal function success. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0021 [18]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	0.3142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0954
upper limit	0.533
Variability estimate	Standard error of the mean
Dispersion value	0.0927

Notes:

[18] - Wald’s z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective).

Statistical analysis title	NI/S of HD Osteogrow vs SoC: LPRS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and unadjusted LPRS rates were pooled according to Rubin’s rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	non-inferiority[19]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	31.2
Confidence interval	
level	95 %
sides	1-sided
lower limit	16

Notes:

[19] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	NI/S of HD Osteogrow vs SoC: LPRS at 12 months

Statistical analysis description:

Same as for the LPRS analysis at 20 months.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)

Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	superiority
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	7.1
Confidence interval	
level	95 %
sides	1-sided
lower limit	-9.5

Secondary: Quality of life (QoL): Physical component summary (PCS) scores over time

End point title	Quality of life (QoL): Physical component summary (PCS) scores over time

End point description:

General health status and patient satisfaction with their health were assessed by measuring health-related QoL using the 36-Item Short Form Health Survey (SF36). The SF36 PCS score is an indicator of overall physical health (a score of 50 is a norm; values <50 or >50 are below or above the norm, respectively).
For the main arms (SoC and HD Osteogrow), missing PCS scores were imputed by visit using multiple imputation by chained equations (MICE); the predictive mean matching was employed with 5 donor values and the following predictor variables: treatment arm, ODI, "no evidence of motion", neurological success, baseline PCS score, age, smoking, body mass index, and sex. The mean covariate-adjusted scores derived from 20 imputed datasets are shown below. Unadjusted mean scores for all arms, based on actual observations only, are shown in the attachment.

End point type	Secondary

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Score points				
least squares mean (standard error)				
Week 3	32.3 (± 0.97)	32.2 (± 0.95)		
Week 6	34.3 (± 0.92)	35.5 (± 0.95)		
Month 3	37.7 (± 1.04)	36.6 (± 1.04)		
Month 6	36.8 (± 1.14)	38.5 (± 1.12)		
Month 12	38.2 (± 1.40)	40.5 (± 1.46)		
Month 20	36.9 (± 1.52)	42.1 (± 1.45)		

Attachments (see zip file)	Longitudinal analysis of PCS scores/Figure 14.3.19.2.pdf

Statistical analyses

Statistical analysis title	PCS scores over time: Month 20

Statistical analysis description:

PCS scores were modelled and compared between the main arms in the same manner as described for ODI over time.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.0421 [21]
Method	GLS-fitted MMRM
Parameter estimate	Mean difference (final values)
Point estimate	5.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.976
upper limit	9.26
Variability estimate	Standard error of the mean
Dispersion value	2.09

Notes:

[20] - Results for earlier time points are shown in the attachment.

[21] - Wald’s t statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at 6, 12 and 20 months as they were most relevant from a clinical perspective).

Secondary: PCS success (PCSS; meaningful improvement in physical health) at 6, 12 and 20 months after surgery

End point title	PCS success (PCSS; meaningful improvement in physical health) at 6, 12 and 20 months after surgery

End point description:

PCSS was an indicator of relevant improvement in physical health in individual subjects and was defined as a clinically meaningful increase in PCS score of ≥5 points from baseline.
All comparisons were limited to the main arms (SoC and HD Osteogrow) where missing PCS scores were imputed as described for PCS scores over time. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in all arms at all time points, based on the total number of actual observations and interpreted as observed probabilities, are shown in the attachment.

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of patients				
number (not applicable)				
Month 6	61.4	63.4		
Month 12	59.5	66.4		
Month 20	54.9	76.7		

Attachments (see zip file)	Longitudinal analysis of PCS success rates/Figure 14.3.21.1.pdf

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: PCSS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and PCSS rates were pooled according to Rubin's rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	21.8
Confidence interval	
level	95 %
sides	1-sided
lower limit	6.2

Notes:

[22] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	NI/S of HD Osteogrow vs SoC: PCSS at 12 months

Statistical analysis description:

Same as for the PCSS analysis at 20 months.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	7
Confidence interval	
level	95 %
sides	1-sided
lower limit	-9.6

Statistical analysis title	Age-adjusted PCSS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of PCSS over time were modeled and compared between the main arms in the same manner as described for spinal function success. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0395 [23]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	0.2299

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.00845
upper limit	0.451
Variability estimate	Standard error of the mean
Dispersion value	0.0937

Notes:

[23] - Wald’s z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective).

Secondary: Quality of life (QoL): Mental component summary (MCS) scores over time

End point title	Quality of life (QoL): Mental component summary (MCS) scores over time

End point description:

General health status and patient satisfaction with their health were assessed by measuring health-related QoL using the 36-Item Short Form Health Survey (SF36). The SF36 MCS score is an indicator of overall mental health (a score of 50 is a norm; values <50 or >50 are below or above the norm, respectively).
For the main arms (SoC and HD Osteogrow), missing MCS scores were imputed by visit using multiple imputation by chained equations (MICE); the predictive mean matching was employed with 5 donor values and the following predictor variables: treatment arm, ODI, ODI Pain score, LLQ Pain score, baseline MCS score, age, smoking, body mass index, and sex. The mean covariate-adjusted scores derived from 20 imputed datasets are shown below. Unadjusted mean scores for all arms, based on actual observations only, are shown in the attachment.

End point type	Secondary

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Score points				
least squares mean (standard error)				
Week 3	36.6 (± 1.76)	36.5 (± 1.70)		
Week 6	41.2 (± 1.71)	38.9 (± 1.73)		
Month 3	40.6 (± 1.85)	40.1 (± 1.87)		
Month 6	40.2 (± 1.86)	40.4 (± 1.85)		
Month 12	39.2 (± 1.97)	43.1 (± 1.99)		
Month 20	37.7 (± 1.98)	41.8 (± 1.90)		

Attachments (see zip file)	Longitudinal analysis of MCS scores/Figure 14.3.22.2.pdf

Statistical analyses

Statistical analysis title	MCS scores over time: Month 20

Statistical analysis description:

MCS scores were modelled and compared between the main arms in the same manner as described for

ODI over time.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.3344 [25]
Method	GLS-fitted MMRM
Parameter estimate	Mean difference (final values)
Point estimate	4.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	10.86
Variability estimate	Standard error of the mean
Dispersion value	2.8

Notes:

[24] - Results for earlier time points are shown in the attachment.

[25] - Wald’s t statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at 6, 12 and 20 months as they were most relevant from a clinical perspective).

Secondary: MCS success (MCSS; meaningful improvement in mental health) at 6, 12 and 20 months after surgery

End point title	MCS success (MCSS; meaningful improvement in mental health) at 6, 12 and 20 months after surgery

End point description:

MCSS was an indicator of relevant improvement in mental health in individual subjects and was defined as a clinically meaningful increase in MCS score of ≥3 points from baseline.
All comparisons were limited to the main arms (SoC and HD Osteogrow) where missing PCS scores were imputed as described for PCS scores over time. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in all arms at all time points, based on the total number of actual observations and interpreted as observed probabilities, are shown in the attachment.

End point type	Secondary

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of patients				
number (not applicable)				
Month 6	54.6	55.8		
Month 12	43.5	55.7		
Month 20	53.1	51.2		

Attachments (see zip file)	Longitudinal analysis of MCS success rates/Figure 14.3.24.1.

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: MCSS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and PCSS rates were pooled according to Rubin's rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	-1.9
Confidence interval	
level	95 %
sides	1-sided
lower limit	-19.4

Notes:

[26] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	Age-adjusted MCSS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of MCSS over time were modeled and compared between the main arms in the same manner as described for spinal function success. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9999 [27]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.256
upper limit	0.246
Variability estimate	Standard error of the mean
Dispersion value	0.106

Notes:

[27] - Wald's z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective).

Secondary: Neurological success (NS) over time

End point title	Neurological success (NS) over time

End point description:

NS was a component of overall clinical success and was defined as maintenance or improvement in neurological status, i.e., no worsening in the American Spinal Injury Association (ASIA) motor and sensory scores for lower extremities, patellar and Achilles reflexes, and straight leg raise test results (all on both sides, left and right), with no new permanent neurological deficit related to treated spinal level. For the main arms (SoC, HD Osteogrow), missing binary data on NS (Yes/No) were imputed by visit using MICE, based on logistic regression and the following predictor variables: treatment arm, "no evidence of motion", any unintended ossification, ODI, SF36 PCS score, age, smoking, BMI, and sex. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in

all arms (based on the number of subjects who completed the visit; those with missing data counted as non-success), interpreted as observed probabilities, are shown in the attachment.

End point type	Secondary

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)				
Week 3	43.4	40.0		
Week 6	36.8	52.6		
Month 3	34.1	46.1		
Month 6	49.9	38.8		
Month 12	38.2	29.3		
Month 20	50.0	39.1		

Attachments (see zip file)	Longitudinal analysis of neurological success rate/Figure

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: NS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and the results were pooled according to Rubin’s rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[28]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	-10.9
Confidence interval	
level	95 %
sides	1-sided
lower limit	-27.2

Notes:

[28] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	Age-adjusted NS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of NS over time were modeled and compared between the main arms in the same manner as described for spinal function success. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6283 [29]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	-0.1056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.341
upper limit	0.1302
Variability estimate	Standard error of the mean
Dispersion value	0.099

Notes:

[29] - Wald's z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective); unadjusted p=0. 2859.

Secondary: Incidence of adverse events (AEs) and treatment-emergent adverse events (TEAEs)

End point title	Incidence of adverse events (AEs) and treatment-emergent adverse events (TEAEs)

End point description:

AEs were collected at each post-screening visit. TEAEs were defined as any AEs that occurred after the start of study treatment, i.e., after placement of an implant (Osteogrow or autologous bone graft [ABG]) into the lateral gutter. Each AE/TEAE was categorized by seriousness, severity, outcome, and relationship to each the implant (Osteogrow or ABG) and surgical procedure (SP; surgery on Day 0). Categorization was to be performed by a blinded evaluator, but this could not be confirmed for all events. The categories shown in endpoint values are not mutually exclusive but include all events that met the criteria for a given category, e.g., deaths were also counted as serious TEAEs, or "implant- and SP-related AEs" were also counted as both implant-related and SP-related AEs. Consequently, implant-related SAEs were equivalent to the SAE component of overall clinical success (implant- or implant/surgical procedure-associated SAEs).

End point type	Secondary

End point timeframe:

From screening until the end of observation (up to 20 months after surgery)

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	61	20	
Units: Percentage of subjects				
number (confidence interval 95%)				
Any adverse event (AE)	98.4 (91.3 to 99.7)	90.2 (80.2 to 95.4)	90.0 (69.9 to 97.2)	
Any treatment-emergent AE (TEAE)	98.4 (91.3 to 99.7)	90.2 (80.2 to 95.4)	85.0 (64.0 to 94.8)	
Serious TEAEs	54.1 (41.7 to 66.0)	31.1 (20.9 to 43.6)	25.0 (11.2 to 46.9)	
Severe TEAEs	44.3 (32.5 to 56.7)	19.7 (11.6 to 31.3)	10.0 (2.8 to 30.1)	
Any implant-related AEs	4.9 (1.7 to 13.5)	6.6 (2.6 to 15.7)	5.0 (0.9 to 23.6)	

Any surgical procedure-related AEs	52.5 (40.2 to 64.5)	45.9 (34.0 to 58.3)	40.0 (21.9 to 61.3)	
Implant and procedure-related AEs	3.3 (0.9 to 11.2)	6.6 (2.6 to 15.7)	5.0 (0.9 to 23.6)	
Surgical procedure-related SAEs	13.1 (6.8 to 23.8)	11.5 (5.7 to 21.8)	15.0 (5.2 to 36.0)	
Non-TEAEs	6.6 (2.6 to 15.7)	3.3 (0.9 to 11.2)	15.0 (5.2 to 36.0)	

Statistical analyses

Statistical analysis title	Any adverse events (main arms)

Statistical analysis description:

Wilson’s 95% CIs were calculated for within-arm percentages to avoid a negative lower bound and provide a more accurate estimate in the case of low fraction of events. The comparison was limited to the main arms; the 95% CI for the SoC - HD Osteogrow difference in percentages was calculated using the Miettinen-Nurminen method to provide a more accurate and conservative estimate in the case of low event fraction or small differences between the arms. CIs were not adjusted for multiplicity.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other[30]
Parameter estimate	Difference in percentages
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	18.5

Notes:

[30] - The difference is statistically significant if the CI does not include zero.

Statistical analysis title	Any TEAEs (main arms)

Statistical analysis description:

Same as for analysis of any adverse events.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	18.5

Statistical analysis title	Serious TEAEs (main arms)

Statistical analysis description:

Same as for analysis of any adverse events. Three subjects in the SoC arm died (4.9%; 95%CI: 1.7% to 13.5%) vs. none in the Osteogrow arms (0%; 95%CI: not calculated).

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	39.2

Statistical analysis title	Severe TEAEs (main arms)

Statistical analysis description:

Same as for analysis of any adverse events.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	24.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.1
upper limit	40

Statistical analysis title	Implant-related AEs (main arms)

Statistical analysis description:

Same as for analysis of any adverse events. Implant-related AEs were serious in one subject in the SoC arm (1.6%; 95%CI: 0.3% to 8.7%) vs. none in the Osteogrow arms (0%; 95%CI: not calculated).

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	7.9

Statistical analysis title	Surgical procedure-related AEs (main arms)
Statistical analysis description: Same as for analysis of any adverse events.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	23.9

Statistical analysis title	Implant- and procedure-related AEs (main arms)
Statistical analysis description: Same as for analysis of any adverse events.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.9
upper limit	5.5

Statistical analysis title	Surgical procedure-related SAEs (main arms)
Statistical analysis description: Same as for analysis of any adverse events.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	14.1

Statistical analysis title	Non-TEAEs (main arms)
Statistical analysis description:	
Same as for analysis of any adverse events.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentages
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	12.9

Secondary: Additional surgical procedures related to the treated spinal level (ASP): Incidence

End point title	Additional surgical procedures related to the treated spinal level (ASP): Incidence
End point description:	
Additional surgical procedures related to the treated spinal level included all minor or major subsequent procedures in the area of the surgical wound or the treated spinal segment, regardless of whether they were triggered by complications of PLIF surgery or unsatisfactory therapeutic response to PLIF surgery. All comparisons were limited to the main arms (SoC and HD Osteogrow).	
End point type	Secondary
End point timeframe:	
From surgery (Day 0) until the end of observation (up to 20 months after surgery)	

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)	LD Osteogrow (mITT)	Standard of Care (SAF)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	56	19	61
Units: Percentage of subjects				
number (not applicable)	14.5	8.9	5.3	14.8

End point values	HD Osteogrow (SAF)	LD Osteogrow (SAF)		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	20		
Units: Percentage of subjects				
number (not applicable)	11.5	5.0		

Statistical analyses

Statistical analysis title	ASP (main arms): Incidence, mITT

Statistical analysis description:

Logistic regression with treatment arm as the only categorical covariate.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3566
Method	Regression, Logistic

Statistical analysis title	ASP (main arms): Incidence, SAF

Statistical analysis description:

Logistic regression with treatment arm as the only categorical covariate.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5912
Method	Regression, Logistic

Secondary: Additional surgical procedures related to the treated spinal level (ASP): Number of additional procedures

End point title	Additional surgical procedures related to the treated spinal level (ASP): Number of additional procedures

End point description:

End point type	Secondary

End point timeframe:

From surgery (Day 0) until the end of observation (up to 20 months after surgery)

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)	LD Osteogrow (mITT)	Standard of Care (SAF)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	56	19	61
Units: Percentage of subjects	10	6	2	11

End point values	HD Osteogrow (SAF)	LD Osteogrow (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	20		
Units: Percentage of subjects	10	2		

Statistical analyses

Statistical analysis title	ASP (main arms): Number of procedures, mITT

Statistical analysis description:

The average number of additional procedures per arm was calculated for all arms (termed procedure-per-patient ratio: 0.182 vs. 0.107 and 0.105 in the SoC vs. HD and LD Osteogrow arms, respectively) and compared between the main arms using a Poisson generalized linear model (GLM). The fitted model was tested for overdispersion and was found appropriate.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3013
Method	Poisson GLM

Statistical analysis title	ASP (main arms): Number of procedures, SAF

Statistical analysis description:

The average number of additional procedures per arm was calculated for all arms (termed procedure-per-patient ratio: 0.180 vs. 0.164 and 0.100 in the SoC vs. HD and LD Osteogrow arms, respectively) and compared between the main arms using a negative binomial GLM because the Poisson GLM did not pass the criteria for overdispersion.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.8557
Method	Negative binomial GLM

Notes:

[31] - Negative binomial GLM

Secondary: Pelvic/hip pain over time

End point title	Pelvic/hip pain over time

End point description:

Data on postoperative pelvic/hip pain, a proxy for iliac crest pain, were collected from hospital discharge

onwards. Pain was quantified using the HOOS Pain score (range 0 to 100), the score for the pain domain of the Hip Dysfunction and Osteoarthritis Outcome Score questionnaire (questions P1 to P10). Higher HOOS Pain scores indicate less pain. As for other endpoints, all comparisons were limited to the main arms (SoC and HD Osteogrow).

End point type	Secondary

End point timeframe:

Hospital discharge, weeks 3 and 6, and months 3, 6, 12 and 20

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	59[32]	61[33]	19[34]	
Units: Score points				
arithmetic mean (standard deviation)				
Discharge	74.5 (± 21.8)	68.1 (± 26.5)	62.4 (± 23.4)	
Week 3	70.4 (± 24.7)	69.7 (± 25.3)	66.1 (± 22.8)	
Week 6	74.9 (± 22.5)	73.1 (± 24.7)	72.2 (± 26.4)	
Month 3	71.9 (± 25.5)	70.9 (± 27.0)	69.9 (± 26.1)	
Month 6	71.8 (± 25.6)	73.5 (± 27.6)	69.7 (± 28.0)	
Month 12	66.5 (± 27.9)	79.4 (± 22.6)	68.7 (± 29.0)	
Month 20	67.1 (± 24.6)	80.3 (± 22.2)	71.6 (± 20.8)	

Notes:

[32] - 59, 57, 55, 54, 54, 50 and 51 at discharge, week 3, week 6 and months 3, 6, 12 and 20, respectively
[33] - 61, 59, 58, 55, 56, 50 and 52 at discharge, week 3, week 6 and months 3, 6, 12 and 20, respectively
[34] - 19, 17, 18, 19, 18, 19 and 18 at discharge, week 3, week 6 and months 3, 6, 12 and 20, respectively

Attachments (see zip file)	Longitudinal analysis of HOOS Pain scores/Figure 14.4.54.2.pdf

Statistical analyses

Statistical analysis title	HD Osteogrow vs SoC: Pelvic/hip pain at 20 months

Statistical analysis description:

Exploratory superiority testing was based on the 1-sided 95% CI for the HD Osteogrow - SoC difference in mean unadjusted HOOS Pain scores, calculated using a t-test with Welch–Satterthwaite adjustment for degrees of freedom. The lower limit of this CI >0 indicated superiority. A fixed testing sequence (starting at month 20 and continuing backward until discharge) was applied, stopping after the first non-rejection of the null hypothesis and leaving the remaining hypotheses non-rejected.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	13.2
Confidence interval	
level	95 %
sides	1-sided
lower limit	5.5

Statistical analysis title	HD Osteogrow vs SoC: Pelvic/hip pain at 12 months
Statistical analysis description: The same as described for pelvic/hip pain at 20 months.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	12.9
Confidence interval	
level	95 %
sides	1-sided
lower limit	4.3

Statistical analysis title	HD Osteogrow vs SoC: Pelvic/hip pain at 6 months
Statistical analysis description: The same as described for pelvic/hip pain at 20 months.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	1-sided
lower limit	-6.7

Statistical analysis title	HOOS Pain scores over time (main arms): Month 20
Statistical analysis description: HOOS Pain scores over time were modeled for the main arms using GLS-fitted MMRM, a fixed-effect general linear model for repeated measurements with Kenward-Roger adjustment for degrees of freedom, REML estimation of the (co)variance parameters, unstructured covariance pattern, and adjustment for age, allowing the adjustments to vary at each time point. The obtained estimates were compared between arms at each visit using Wald’s t statistic; 2-sided tests at α=0.05.	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.0455 [36]
Method	GLS-fitted MMRM
Parameter estimate	Mean difference (final values)
Point estimate	9.611

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.197
upper limit	19.03
Variability estimate	Standard error of the mean
Dispersion value	4.75

Notes:

[35] - Wald’s t statistic (Kenward-Roger scaled Wald’s statistic) is adjusted through both the denominator degrees of freedom and appropriate inflation of the variance-covariance matrix, accounting for small sample sizes and mild deviations from normality of the normalized model residuals. P-values and 95% CIs for mean HD Osteogrow-SoC differences were both unadjusted and adjusted for multiplicity using the mvt method. Results for earlier time points are shown in the attachment.
[36] - Wald’s t statistic unadjusted for multiplicity; p=0.1785 after mvt correction for 7 tests.

Secondary: Anti-rhBMP antibodies

End point title	Anti-rhBMP antibodies

End point description:

Anti-rhBMP6 antibodies were measured at screening and 3, 6, 12 and 20 months after surgery using a validated indirect enzyme-linked immunosorbent assay. Test results were reported as positive, negative, or indeterminate. At least one postoperative test result was available for 58 (95%), 57 (93%) and 19 (95%) subjects in the SoC, HD Osteogrow and LD Osteogrow arms, respectively. The endpoint values shown below are percentages of subjects tested positive for anti-rhBMP6 antibodies, calculated based on the total number subjects tested at each time point. No subject had an indeterminate test result.

End point type	Secondary

End point timeframe:

3, 6, 12 and 20 months after surgery

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	60[37]	59[38]	20[39]	
Units: Percentage of subjects				
number (not applicable)				
Screening	0.0	0.0	0.0	
Month 3	0.0	0.0	0.0	
Month 6	0.0	0.0	0.0	
Month 12	0.0	0.0	0.0	
Month 20	0.0	0.0	0.0	

Notes:

[37] - 60, 52, 54, 49 and 47 subjects had data at screening and months 3, 6, 12 and 20, respectively

[38] - 59, 53, 51, 48 and 48 subjects had data at screening and months 3, 6, 12 and 20, respectively

[39] - : 20, 18, 17, 18 and 18 subjects had data at screening and months 3, 6, 12 and 20, respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Operative time

End point title	Operative time

End point description:

Operative time was defined as the time from the first surgical incision to closure of the surgical wound.

End point type	Secondary
End point timeframe:	
Day of surgery (Day 0)	

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	61	20	
Units: Minutes				
arithmetic mean (standard deviation)	198.4 (± 68.9)	169.1 (± 155.0)	165.4 (± 60.4)	

Statistical analyses

Statistical analysis title	Operative time (main arms)
Statistical analysis description:	
Operative time was compared between the main arms using the Monte-Carlo (permutation) version of the Welch t-test (9999 samples, seed=1000).	
Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0072
Method	Permutation Welch two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	29.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.64
upper limit	50.82
Variability estimate	Standard error of the mean
Dispersion value	11.132

Secondary: Intraoperative blood loss

End point title	Intraoperative blood loss
End point description:	
Intraoperative blood loss was estimated using the Lopez-Pikado equation, based on hematocrit before surgery and on postoperative day 5, blood transfusions during surgery and up to day 5, and sex, age, body weight and height of the subject.	
End point type	Secondary
End point timeframe:	
Day of surgery (Day 0)	

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	61	20	
Units: Milliliters				
arithmetic mean (standard deviation)	1425.2 (± 482.2)	1318.3 (± 473.2)	1361.5 (± 445.2)	

Statistical analyses

Statistical analysis title	Intraoperative blood loss (main arms)

Statistical analysis description:

Blood loss was compared between the main arms using the Monte-Carlo (permutation) version of the Welch t-test (9999 samples, seed=1000).

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2528
Method	Permutation Welch two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	107.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.11
upper limit	287.62
Variability estimate	Standard error of the mean
Dispersion value	92.518

Secondary: Number of hospital days

End point title	Number of hospital days

End point description:

End point type	Secondary

End point timeframe:

From the day of surgery (Day 0) until the end of observation (up to 20 months)

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	61	20	
Units: Days				
arithmetic mean (standard deviation)				
Initial postoperative hospital stay	8.8 (± 3.5)	8.3 (± 3.1)	8.6 (± 4.7)	
All hospital stays during follow-up	22.6 (± 18.9)	20.2 (± 15.1)	15.6 (± 11.2)	

Statistical analyses

Statistical analysis title	Postoperative hospital stay (main arms)

Statistical analysis description:

The length of postoperative hospital stay was compared between the main arms using the Monte-Carlo (permutation) version of the Welch t-test (9999 samples, seed=1000).

Comparison groups	HD Osteogrow (SAF) v Standard of Care (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3428
Method	Permutation Welch two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.562
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.627
upper limit	1.704
Variability estimate	Standard error of the mean
Dispersion value	0.598

Statistical analysis title	All hospital stays during follow-up (main arms)

Statistical analysis description:

The same as described above for postoperative hospital stay.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4267
Method	Permutation Welch two-sample t-test
Parameter estimate	Mean difference (final values)
Point estimate	2.499
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.661
upper limit	8.644

Variability estimate	Standard error of the mean
Dispersion value	3.149

Other pre-specified: "No evidence of motion" at the treated spinal level

End point title	"No evidence of motion" at the treated spinal level

End point description:

"No evidence of motion" (NEoM) at the treated spinal level was a component of radiographic fusion and defined as ≤3 mm translation and <5 degrees angular motion on lateral flexion/extension x-rays. Motion was measured with FXA™ software.
For the main arms (SoC, HD Osteogrow), missing binary data on NEoM (Yes/No) at 6, 12 and 20 months were imputed by visit using MICE, based on logistic regression and the following predictor variables: treatment arm, bridging on either side, ODI, neurological success, SF36 PCS score, age, smoking, BMI, and sex. As NEoM was used as a predictor for some other variables, data for earlier time points were imputed by carrying backward the first postoperative value.
The endpoint values shown below are estimated marginal means (EM means) from the model described in the statistical analysis section. The observed NEoM rates in all arms, based on the total number of actual observations and interpreted as observed probabilities, are shown in the attachment.

End point type	Other pre-specified

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Unitless (range 0 to 1)				
number (confidence interval 95%)				
Month 6	0.958 (0.818 to 0.992)	0.942 (0.812 to 0.985)		
Month 12	0.956 (0.774 to 0.994)	0.900 (0.776 to 0.966)		
Month 20	0.970 (0.787 to 0.997)	0.942 (0.808 to 0.987)		

Attachments (see zip file)	Longitudinal analysis of no evidence of motion/Figure 14.3.3.1.

Statistical analyses

Statistical analysis title	"No evidence of motion": Month 20

Statistical analysis description:

Probabilities of "no evidence of motion" were modeled for each of the 20 imputed datasets using GEE-estimated logistic regression (unstructured covariance, age and baseline value interacting with visit), pooled, and compared between arms at each visit on a probability scale (marginal means estimated on a response scale) using Wald's z statistic (asymptotic normal approximation of the distribution of the relevant test statistic under infinite degrees of freedom); 2-sided tests at α=0.05.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.888 [41]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	-0.0283
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.133
upper limit	0.0768
Variability estimate	Standard error of the mean
Dispersion value	0.0441

Notes:

[40] - P-values and 95% CIs for mean (pooled) HD Osteogrow - SoC differences were both unadjusted and adjusted for multiplicity using the so-called mvt method, a parametric exact method where the critical value for the test statistic is derived from the multivariate t distribution accounting for the estimated means and covariances. Results for earlier time points are shown in the attachment.
[41] - Wald's z statistic with mvt correction for 3 tests.

Other pre-specified: Bony bridging on at least one side

End point title	Bony bridging on at least one side

End point description:

Bony bridging was defined as radiographic evidence of continuous bony connection from the superior to inferior transverse process. It was assessed separately for the left/right side by consensus of 3 blinded assessors. Bilateral bridging was required to claim the radiographic fusion, yet any bridging was also of interest.
For the main arms (SoC, HD Osteogrow), missing data at 6, 12 or 20 months were imputed separately for each side using MICE, by logistic regression and the following predictor variables: treatment arm, "no evidence of motion", ODI, neurological success, SF36 PCS score, age, smoking, BMI, and sex. The presence of unilateral or bilateral bridging was passively imputed thereafter by logical conjunction of the data for each side.
The endpoint values are estimated marginal means (EM means) from the model described in the statistical analysis section. The observed bridging rates in all arms, based on the total number of actual observations, are shown in the attachment.

End point type	Other pre-specified

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Unitless (range 0 to 1)				
arithmetic mean (standard error)				
Month 6	0.265 (± 0.0595)	0.158 (± 0.0518)		
Month 12	0.347 (± 0.0762)	0.159 (± 0.0545)		
Month 20	0.360 (± 0.0717)	0.148 (± 0.0525)		

Attachments (see zip file)	Longitudinal analysis bridging on at least 1 side/Figure

Statistical analyses

Statistical analysis title	Bridging on at least one side: Month 20

Statistical analysis description:

Probabilities of at least unilateral bridging were modeled for each of the 20 imputed datasets using GEE-estimated logistic regression (unstructured covariance; age interacting with visit), pooled, and compared between arms at each visit on a probability scale (marginal means estimated on a response scale) using Wald's z statistic (asymptotic normal approximation of the distribution of the relevant test statistic under infinite degrees of freedom); 2-sided tests at α=0.05.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.045 [43]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	-0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.419
upper limit	-0.00366
Variability estimate	Standard error of the mean
Dispersion value	0.0885

Notes:

[42] - P-values and 95% CIs for mean (pooled) HD Osteogrow-SoC differences were both unadjusted and adjusted for multiplicity as described for "no evidence of motion". Results for earlier time points are shown in the attachment.
[43] - Wald's z statistic with mvt correction for 3 tests.

Other pre-specified: Bilateral bony bridging

End point title	Bilateral bony bridging

End point description:

Bilateral bony bridging, defined as radiographic evidence of continuous bony connection from the superior to inferior transverse process on both sides, was a component of radiographic fusion.
For the main arms (SoC, HD Osteogrow), missing data at 6, 12 or 20 months were imputed as described for "bony bridging on at least one side". The resulting data on bilateral bridging were used to calculate radiographic fusion rates in the imputed dataset but were not separately analysed. Namely, the planned longitudinal modelling was omitted due to low rates of bilateral bridging in the non-imputed mITT dataset which are shown below. No bilateral bridging was observed in the LD Osteogrow arm at any time point.

End point type	Other pre-specified

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[44]	50[45]		
Units: Percentage of subjects				
number (not applicable)				
Month 6	3.7	5.7		
Month 12	4.3	6.0		
Month 20	6.4	4.0		

Notes:

[44] - Subjects from the mITT dataset with actual observations at months 12 or 20 (54 at month 6)

[45] - Subjects from the mITT dataset with actual observations at months 12 or 20 (53 at month 6)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of new permanent neurological deficits

End point title	Incidence of new permanent neurological deficits

End point description:

Neurological status was assessed at screening, before surgery (only for subjects screened >7 days before surgery), on the day of hospital discharge, and 3 weeks, 6 weeks and 3, 6, 12 and 20 months after surgery. A new permanent neurological deficit was defined as any neurological deficit observed at the last subject's visit, unless it was already present before surgery or was obviously unrelated to the treated spinal level in the investigator's opinion.

End point type	Other pre-specified

End point timeframe:

End of observation (up to 20 months after surgery)

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	61	20	
Units: Percentage of subjects				
number (not applicable)	11.5	4.9	10.0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of surgical site swelling/edema

End point title	Incidence of surgical site swelling/edema

End point description:

Surgical site swelling/edema was assessed by a blinded evaluator and categorized as absent, mild, moderate, or severe. The endpoint values shown below and analysed are the percentages of subjects

with swelling/edema of any severity, calculated based on the number of actual observations (severe swelling/edema was reported in only one subject in the SoC arm and one in the LD Osteogrow arm). Given that this variable, dichotomised into "Absent/Present", was one of the predictors for imputation of missing ODI Pain scores, missing data on surgical site swelling/edema in the mITT dataset for the main arms (SoC and HD Osteogrow) were imputed as follows: (a) from month 6 onwards, "Absent" was imputed, unless the preceding or subsequent observed value was "Present" (the latter was imputed in this case); (b) from week 3 to month 3 inclusive, the last observation was carried forward and then the next observation was carried backward for the remaining missing values.

End point type	Other pre-specified

End point timeframe:

Hospital discharge, weeks 3 and 6, and months 3, 6, 12 and 20

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61[46]	61[47]	19[48]	
Units: Percentage of subjects				
number (not applicable)				
Discharge	68.9	75.4	57.9	
Week 3	43.1	41.4	35.3	
Week 6	17.2	6.8	11.1	
Month 3	1.8	1.8	5.6	
Month 6	0.0	0.0	0.0	
Month 12	0.0	0.0	0.0	
Month 20	0.0	0.0	0.0	

Notes:

[46] - 61, 58, 58, 57, 56, 50 and 51 at discharge, week 3, week 6 and months 3, 6, 12 and 20, respectively
[47] - 61, 58, 59, 56, 54, 50 and 51 at discharge, week 3, week 6 and months 3, 6, 12 and 20, respectively
[48] - 19, 17, 18, 18, 17, 18 and 18 at discharge, week 3, week 6 and months 3, 6, 12 and 20, respectively

Attachments (see zip file)	Percentage of patients with surgical site swelling/Figure

Statistical analyses

Statistical analysis title	Adjusted probability of swelling/edema: Discharge

Statistical analysis description:

The comparison was limited to the main arms. For each time point, the age-adjusted probability of surgical site swelling/edema was estimated by logistic regression and compared between arms on a probability scale (marginal means estimated on a response scale) using Wald's z statistic (asymptotic normal approximation of the distribution of the relevant test statistic under infinite degrees of freedom); 2-sided tests at $\alpha=0.05$.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.4938 [50]
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	0.0559

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.2016
Variability estimate	Standard error of the mean
Dispersion value	0.0817

Notes:

[49] - P-values were both unadjusted and adjusted for multiplicity using the Holm method. Results for other time points are shown in the attachment.
[50] - Wald's z statistic unadjusted for multiplicity.

Other pre-specified: Incidence of unintended soft tissue ossification (USTO)

End point title	Incidence of unintended soft tissue ossification (USTO)

End point description:

USTO was assessed by 3 blinded assessors on CT scans or lumbar spine x-rays, if CT was not available, and was considered present if reported by at least 2 assessors. It was categorized as distant (if observed in the lateral gutter of adjacent spinal segments or beyond the line connecting the lateral edges of transverse processes at the treated or adjacent segments), medially spreading (if reaching neuroforamina or spinal canal), or "other" (if observed elsewhere). The endpoint values shown below were calculated based on the number of actual observations.
Given that USTO (any type) was one of the predictors used for MICE, missing USTO data in the mITT dataset for the main arms (SoC and HD Osteogrow) were imputed as follows: a) from week 3 to month 3, "Absent" was imputed by default; b) from month 6 onwards, the last observation was carried forward and then the next observation was carried backward where applicable; if there were no data to carry in any direction, "Absent" was imputed.

End point type	Other pre-specified

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (SAF)	HD Osteogrow (SAF)	LD Osteogrow (SAF)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57[51]	55[52]	19[53]	
Units: Percent of patients				
number (not applicable)				
Distant ossification: Month 6	1.8	1.9	5.6	
Distant ossification: Month 12	2.0	9.8	0.0	
Distant ossification: Month 20	2.0	3.9	5.6	
Distant ossification: Subject's last visit	1.8	16.7	11.1	
Medially spreading: Month 6	0.0	1.9	0.0	
Medially spreading: Month 12	0.0	2.0	0.0	
Medially spreading: Month 20	0.0	0.0	0.0	
Medially spreading: Subject's last visit	0.0	0.0	0.0	
Other unintended: Month 6	1.8	3.7	0.0	
Other unintended: Month 12	2.0	3.9	0.0	
Other unintended: Month 20	4.0	17.6	5.6	
Other unintended: Subject's last visit	3.5	18.2	5.3	
Any of the above: Month 6	3.5	7.4	5.6	
Any of the above: Month 12	4.0	13.7	0.0	
Any of the above: Month 20	6.0	21.6	11.1	
Any of the above: Subject's last visit	5.3	21.8	10.5	

Notes:

[51] - 57 for the subject's last visit, and 57, 50 and 50 for months 6, 12 and 20, respectively

[52] - 55 for the subject's last visit, and 54, 51 and 51 for months 6, 12 and 20, respectively

[53] - 19 for the subject's last visit, and 18, 19 and 18 for months 6, 12 and 20, respectively

Statistical analyses

Statistical analysis title	Distant ossification: Overall incidence

Statistical analysis description:

The overall incidence of individual categories of USTO across months 6, 12, 20 was compared between the main arms using a logistic regression model (treatment arm interacted with USTO category allowing the effect to vary across categories) and Wald's z statistic; 2-sided tests at α=0.05. CIs were calculated on the logit scale and back transformed. P-values and 95% CIs for SoC - HD Osteogrow differences were both unadjusted and adjusted for multiplicity using the mvt method.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.111 [55]
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.229
upper limit	0.024
Variability estimate	Standard error of the mean
Dispersion value	0.065

Notes:

[54] - For each USTO category, the overall incidence across months 6, 12 and 20 was calculated by combining data for the three visits as follows: it was counted as "present" if detected at any of these visits, and "absent" only if absent at all three visits. Subjects who did not meet these criteria were excluded from the analysis, resulting in an overall incidence of distant ossification of 3/47 (6.4%) in the SoC arm vs. 8/48 (16.7%) and 2/18 (11.1%) in the HD and LD Osteogrow arms, respectively.

[55] - Wald's z statistic unadjusted for multiplicity.

Statistical analysis title	Medially spreading ossification: Overall incidence

Statistical analysis description:

The same as for the analysis of distant ossification.

Comparison groups	Standard of Care (SAF) v HD Osteogrow (SAF)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	= 0.149 [57]
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.098
upper limit	0.015

Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

[56] - For each USTO category, the overall incidence across months 6, 12 and 20 was calculated by combining data for the three visits as follows: it was counted as "present" if detected at any of these visits, and "absent" only if absent at all three visits. Subjects who did not meet these criteria were excluded from the analysis, resulting in an overall incidence of medially spreading USTO of 0/46 (0.0%) in the SoC arm vs. 2/48 (4.2%) and 0/18 (0.0%) in the HD and LD Osteogrow arms, respectively.
[57] - Wald's z statistic unadjusted for multiplicity.

Statistical analysis title	Other unintended ossification: Overall incidence

Statistical analysis description:

The same as for the analysis of distant ossification.

Comparison groups	HD Osteogrow (SAF) v Standard of Care (SAF)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	= 0.041 [59]
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.272
upper limit	-0.005
Variability estimate	Standard error of the mean
Dispersion value	0.068

Notes:

[58] - For each USTO category, the overall incidence across months 6, 12 and 20 was calculated by combining data for the three visits as follows: it was counted as "present" if detected at any of these visits, and "absent" only if absent at all three visits. Subjects who did not meet these criteria were excluded from the analysis, resulting in an overall incidence of "other" USTO of 3/46 (6.5%) in the SoC arm vs. 10/49 (20.4%) and 1/18 (5.6%) in the HD and LD Osteogrow arms, respectively.
[59] - Wald's z statistic unadjusted for multiplicity; p=0.119 after mvt correction for 3 tests.

Statistical analysis title	Any unintended ossification: Overall incidence

Statistical analysis description:

The overall incidence of any USTO across months 6, 12, 20 (distant, medially spreading and "other" USTO combined) was compared between the main arms using the 2-sample Wald's chi-squared test for equality of proportions.

Comparison groups	HD Osteogrow (SAF) v Standard of Care (SAF)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	= 0.0163
Method	Wald's chi-squared test

Notes:

[60] - For any USTO, the overall incidence across months 6, 12 and 20 was calculated by combining data for the three visits as follows: it was counted as "present" if detected at any of these visits, and "absent" only if absent at all three visits. Subjects who did not meet these criteria were excluded from the analysis, resulting in an overall incidence of any USTO of 6/47 (12.8%) in the SoC arm vs. 16/49 (32.7%) and 3/18 (16.7%) in the HD and LD Osteogrow arms, respectively.

Post-hoc: Alternative neurological success (ANS) over time

End point title	Alternative neurological success (ANS) over time

End point description:

Given that the obtained neurological success rates were largely driven by changes in reflexes and inconsistent with other outcomes, e.g., changes in other components of neurological status or overall ratings of neurological status made by the same evaluator, they were recalculated using an alternative definition of neurological success: absence of clinically relevant abnormalities in neurological status with no new permanent neurological deficits.
For the main arms (SoC, HD Osteogrow), missing binary data (Yes/No) were imputed by MICE using the same predictors as for neurological success: treatment arm, "no evidence of motion", any unintended ossification, ODI, SF36 PCS score, age, smoking, BMI, and sex. The endpoint values shown below were pooled from 20 imputed datasets. The observed ANS rates in all arms (based on the number of subjects who completed the visit; those with missing data counted as non-success), interpreted as observed probabilities, are shown in the attachment.

End point type	Post-hoc

End point timeframe:

3 weeks, 6 weeks, and 3, 6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)				
Week 3	81.7	85.3		
Week 6	79.6	86.8		
Month 3	85.3	85.4		
Month 6	83.0	89.1		
Month 12	74.5	91.2		
Month 20	71.4	84.6		

Attachments (see zip file)	Longitudinal analysis of alternative neurological /Figure 14.4.51

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: ANS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and the results were pooled according to Rubin's rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	non-inferiority[61]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	13.2
Confidence interval	
level	95 %
sides	1-sided
lower limit	-1

Notes:

[61] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	Age-adjusted ANS over time: Month 20

Statistical analysis description:

Age-adjusted probabilities of ANS over time were modeled and compared between the main arms in the same manner as described for spinal function success. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.3757 [62]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	0.1162
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.082
upper limit	0.315
Variability estimate	Standard error of the mean
Dispersion value	0.1162

Notes:

[62] - Wald’s z statistic with mvt correction for 3 tests (adjustments for multiplicity were limited to tests at months 6, 12 and 20, the most relevant time points from a clinical perspective); unadjusted p=0. 1679.

Post-hoc: Alternative overall success (AOS) at 6, 12 and 20 months

End point title	Alternative overall success (AOS) at 6, 12 and 20 months

End point description:

Given that overall clinical success (OCS) rates were inconsistent with other findings, success rates were recalculated post-hoc using a less stringent definition of success, termed AOS. AOS had the same components as OCS, but radiographic fusion was defined as “no evidence of motion” at the treated spinal level, and neurological success as the absence of clinically relevant abnormalities in neurological status with no new permanent neurological deficits (alternative neurological success). The remaining three components were the same as for OCS.
For the main arms (SoC and HD Osteogrow), missing data on individual AOS components were imputed using MICE or univariate methods, as described elsewhere. The endpoint values shown below were pooled from 20 imputed datasets. The observed success rates in all arms (based on the number of subjects who completed the visit; those with missing data counted as “failure”), interpreted as observed probabilities, are shown in the attachment.

End point type	Post-hoc

End point timeframe:

6, 12 and 20 months after surgery

End point values	Standard of Care (mITT)	HD Osteogrow (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Pooled percentage of subjects				
number (not applicable)				
Month 6	38.5	44.8		

Month 12	45.5	46.3		
Month 20	39.5	48.2		

Attachments (see zip file)	Longitudinal analysis alternative overall success/Figure

Statistical analyses

Statistical analysis title	NI/S of HD Osteogrow vs SoC: AOS at 20 months

Statistical analysis description:

Each of the 20 imputed datasets was analysed separately and the results were pooled according to Rubin's rules. Exploratory non-inferiority/superiority (NI/S) testing was performed in the same manner as described for radiographic fusion.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[63]
Parameter estimate	Mean (pooled) difference in percentages
Point estimate	8.7
Confidence interval	
level	95 %
sides	1-sided
lower limit	-7.7

Notes:

[63] - The lower limit of the 1-sided 95% CI for the HD Osteogrow - SoC difference greater than -10 percentage points (pp) indicated non-inferiority and the lower limit >0 pp indicated superiority.

Statistical analysis title	Covariate-adjusted AOS over time: Month 20

Statistical analysis description:

Probabilities of AOS over time were modeled and compared between the main arms as described for spinal function success, but adjustments were made for both age and body mass index. Results for all time points are shown in the attachment.

Comparison groups	Standard of Care (mITT) v HD Osteogrow (mITT)
Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.6 [64]
Method	Regression, Logistic
Parameter estimate	Mean difference in probabilities
Point estimate	0.1026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.135
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.1015

Notes:

[64] - Wald's z statistic with mvt correction for 3 tests.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0-20 months

Adverse event reporting additional description:

AEs were collected before and after surgery, at hospital discharge, and 3 weeks, 6 weeks, and 3, 6, 12, and 20 months after surgery. Treatment-emergent AEs (TEAEs), ie, AEs occurring after placement of study implant (Osteogrow or autologous bone graft) into the lateral gutter, were analyzed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Standard of Care

Reporting group description:

360 degrees stabilization with intervertebral cages filled with local (host) bone, instrumentation with pedicle screws, and bilateral autologous bone graft from iliac crest in the lateral gutter (approximately 5 cc per side).

Reporting group title	HD OSTEOGROW

Reporting group description:

Standard of Care plus Osteogrow (1 mg rhBMP6 in 5 mL ABC; 0.2 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 2 mg rhBMP6 in total

Reporting group title	LD OSTEOGROW

Reporting group description:

Standard of Care plus Osteogrow (0.5 mg rhBMP6 in 5 mL ABC; 0.1 mg/mL), supplemented with allograft (1.3 ± 0.2 g of commercially available human cancellous bone granules, 2-8 mm), implanted into each lateral gutter instead of autologous bone graft, 1 mg rhBMP6 in total

Serious adverse events	Standard of Care	HD OSTEOGROW	LD OSTEOGROW
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 61 (54.10%)	20 / 61 (32.79%)	5 / 20 (25.00%)
number of deaths (all causes)	3	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Vulval cancer			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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

Adenocarcinoma of colon			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Breast cancer metastatic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Malignant melanoma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Vascular disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Hypertensive crisis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Peripheral artery occlusion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Carpal tunnel decompression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Knee arthroplasty			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb immobilisation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Peripheral nerve decompression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Medical device implantation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Medical device repositioning			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Hip arthroplasty			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Product issues			
Device fastener issue			
subjects affected / exposed	1 / 61 (1.64%)	3 / 61 (4.92%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Investigations			
Arthroscopy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Cervical vertebral fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Facial bones fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Femoral neck fracture			

subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Meniscus injury			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Post procedural pulmonary embolism			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 61 (1.64%)	2 / 61 (3.28%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Wrist fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Joint dislocation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Post procedural haematoma			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Postoperative wound complication			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Epilepsy			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Hypoaesthesia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Lumbar radiculopathy			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Neuralgia			

subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Cervical spinal stenosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Dizziness			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Muscular weakness			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Gastrointestinal disorders			
Anal incontinence			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Abdominal pain upper			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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			
Arthralgia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 61 (4.92%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Osteoarthritis			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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

Pseudarthrosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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
Pain in extremity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 20 (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
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 20 (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

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

Non-serious adverse events	Standard of Care	HD OSTEOGROW	LD OSTEOGROW
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 61 (98.36%)	55 / 61 (90.16%)	18 / 20 (90.00%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	12 / 61 (19.67%)	10 / 61 (16.39%)	4 / 20 (20.00%)
occurrences (all)	13	10	4

Gamma-GT increased			
subjects affected / exposed	5 / 61 (8.20%)	3 / 61 (4.92%)	1 / 20 (5.00%)
occurrences (all)	5	3	1
Prothrombin time shortened			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Blood immunoglobulin G increased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Glucose urine present			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Platelet count increased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Red blood cell sedimentation rate increased			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Post procedural hypotension			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Postoperative wound complication			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Adjacent segment degeneration			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Post procedural swelling			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 61 (9.84%)	9 / 61 (14.75%)	1 / 20 (5.00%)
occurrences (all)	9	12	1
Nervous system disorders			

Hypoaesthesia			
subjects affected / exposed	3 / 61 (4.92%)	6 / 61 (9.84%)	0 / 20 (0.00%)
occurrences (all)	3	7	0
Sciatica			
subjects affected / exposed	3 / 61 (4.92%)	3 / 61 (4.92%)	1 / 20 (5.00%)
occurrences (all)	4	3	1
Headache			
subjects affected / exposed	4 / 61 (6.56%)	1 / 61 (1.64%)	0 / 20 (0.00%)
occurrences (all)	4	9	0
Dysaesthesia			
subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	1 / 20 (5.00%)
occurrences (all)	2	2	1
Vertigo			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Monoparesis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 61 (3.28%)	3 / 61 (4.92%)	2 / 20 (10.00%)
occurrences (all)	2	3	2
Impaired healing			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			

subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 61 (18.03%)	9 / 61 (14.75%)	1 / 20 (5.00%)
occurrences (all)	12	9	1
Arthralgia			
subjects affected / exposed	6 / 61 (9.84%)	5 / 61 (8.20%)	3 / 20 (15.00%)
occurrences (all)	7	7	4
Pain in extremity			
subjects affected / exposed	4 / 61 (6.56%)	6 / 61 (9.84%)	0 / 20 (0.00%)
occurrences (all)	4	6	0
Osteoarthritis			
subjects affected / exposed	6 / 61 (9.84%)	0 / 61 (0.00%)	0 / 20 (0.00%)
occurrences (all)	6	0	0
Sacral pain			
subjects affected / exposed	5 / 61 (8.20%)	1 / 61 (1.64%)	0 / 20 (0.00%)
occurrences (all)	5	1	0
Osteonecrosis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Metatarsalgia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 61 (6.56%)	5 / 61 (8.20%)	0 / 20 (0.00%)
occurrences (all)	4	5	0
Urinary tract infection			
subjects affected / exposed	5 / 61 (8.20%)	1 / 61 (1.64%)	2 / 20 (10.00%)
occurrences (all)	5	1	3
Nasopharyngitis			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences (all)	2	1	1
Otitis media acute			

subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	4 / 61 (6.56%)	4 / 61 (6.56%)	0 / 20 (0.00%)
occurrences (all)	4	4	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Iron deficiency			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2017	Protocol v5, EC approved on 2.11.2017, initial version
14 March 2018	Protocol v6: Procedures to accommodate adjusted implant application (lowering of implant blood volume), patient blood sampling (anti-rhBMP6 antibody collected from all patients at M24), modification of Box B ancillary items to collect smaller blood amount, adjusted ICF, IB
12 November 2019	Protocol v9, inclusion criterion #5 was relaxed ("healthy" replaced with "in good general condition") as well as exclusion criteria #12 (diabetes mellitus was narrowed to certain clinical types) and #14 (numerical ECG findings were replaced with ECG abnormalities that represent a safety risk for surgery in the investigator's opinion). Hemoglobin A1c was added to the screening tests for subjects with a history of diabetes.
20 December 2019	Protocol v10, reduced sample size from 192 to 134 patients in total (Stage 2 of the trial reduced from 75 to 45, and Stage 3 from 102 to 74), reduced number of treatment arms in Stage 3 from three to two (only one of the two experimental treatment arms will be progressed into Stage 3 based on the outcome of originally planned 2nd safety review by the Independent Drug Safety Monitoring Board; if there is no safety differentiation between the two dose levels, the higher dose will be progressed), reduced power of the trial from 95% to 90%, shortened follow-up period for all patients from 24 to 20 months

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Due to the COVID pandemic urgent safety measures were in effect from mid-March until mid-June 2020. During this period, enrolment was suspended, and follow-up visits were conducted by phone, except for Month 20 visits, which were postponed until the reopening of hospitals for non-emergency patients when these measures were retired.	18 June 2020

Notes:

Limitations and caveats

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

The low overall clinical success rates in all arms, including SoC, indicated an overly strict definition of "success". More realistic estimates were obtained using a less stringent definition of overall success (see alternative overall success).

Notes: