Clinical trial results:
PANSAID – PAracetamol and NSAID in combination: A randomised, blinded, parallel 4-group clinical trial

Summary

EudraCT number	2015-002239-16
Trial protocol	DK
Global end of trial date	01 January 2018

Results information

Result version number	v1 (current)
This version publication date	07 January 2021
First version publication date	07 January 2021

Trial information

Trial identification

Sponsor protocol code	SM2-KHT-2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02571361
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Departement of Anaesthesiology, Næstved Hospital
Sponsor organisation address	Ringstedgade 61, Næstved, Denmark, 4700
Public contact	Department of Anaesthesiology Daniel Hägi-Pedersen, Næstved Hospital, +45 21517167, dhag@regionsjaelland.dk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2018
Global end of trial reached?	Yes
Global end of trial date	01 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to investigate the analgesic effects and safety of paracetamol and ibuprofen and their combination in different dosages after THA

Protection of trial subjects:

Subjects received a Patient Controlled Analgesia Pump with morphine, where they could steer their own pain treatment. Thus reducing patients discomfort in trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 556
Worldwide total number of subjects	556
EEA total number of subjects	556

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	208
From 65 to 84 years	335
85 years and over	13

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All patients planned for total hip arthroplasty

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, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Blinding of trial medication, thus tablets were sealed in opaque hard capsules.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A

Arm description:

Paracetamol 1g + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm type	Active comparator
Investigational medicinal product name	Pinex
Investigational medicinal product code	
Other name	paracetamol
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Paracetamol 1g orally starting1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Investigational medicinal product name	Ibumetin
Investigational medicinal product code	
Other name	Ibumetin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm title	Treatment B

Arm description:

Paracetamol 1g + placebo orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm type	Active comparator
Investigational medicinal product name	Pinex
Investigational medicinal product code	
Other name	paracetamol
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Paracetamol 1g orally starting1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a

total of 4 times the first 24 hours postoperative.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1 capsule placebo orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm title	Treatment C

Arm description:

Placebo + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

2 capsules placebo orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Investigational medicinal product name	Ibumetin
Investigational medicinal product code	
Other name	Ibumetin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm title	Treatment D

Arm description:

Paracetamol 0,5 g + ibuprofen 200 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Arm type	Active comparator
Investigational medicinal product name	Pinex
Investigational medicinal product code	
Other name	paracetamol
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Paracetamol 0,5 g orally starting1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Investigational medicinal product name	Ibumetin
Investigational medicinal product code	
Other name	Ibumetin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibuprofen 200 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.

Number of subjects in period 1	Treatment A	Treatment B	Treatment C
Started	136	142	139
Completed	136	142	139

Number of subjects in period 1	Treatment D
Started	139
Completed	139

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A
Reporting group description:	
Paracetamol 1g + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment B
Reporting group description:	
Paracetamol 1g + placebo orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment C
Reporting group description:	
Placebo + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment D
Reporting group description:	
Paracetamol 0,5 g + ibuprofen 200 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	

Reporting group values	Treatment A	Treatment B	Treatment C
Number of subjects	136	142	139
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	67	67	67
standard deviation	± 10	± 10	± 11
Gender categorical Units: Subjects			
Female	68	66	67
Male	68	76	72
ASA-score			
American Society of Anaesthesiologists Physical Status Classification System			
Units: Subjects			
ASA 1	34	44	44
ASA 2	87	84	80
ASA 3	15	14	15
Anesthesia			
Type of Anesthesia			
Units: Subjects			
Spinal with sedation	65	70	66
Spinal	39	42	43
General	29	20	24
Conversion of spinal to general	3	10	6
Prior use of paracetamol			
Use of paracetamol prior to the operation.			

Units: Subjects			
No use	53	52	51
As needed	29	24	24
Daily use	54	66	64
Prior use of NSAID			
Use of NSAID prior to the operation.			
Units: Subjects			
No use	72	77	74
As needed	21	18	16
Daily use	43	47	49
Prior use of codeine			
Use of codeine prior to the operation			
Units: Subjects			
No use	134	141	136
As needed	1	0	1
Daily use	1	1	2
Prior use of tramadol			
Use of tramadol prior to the operation.			
Units: Subjects			
No use	121	127	125
As needed	5	6	6
Daily use	10	9	8
Type of surgery Units: Subjects			
No cement	122	129	127
Cement	2	3	2
Hybrid	12	10	10
Height Units: cm			
arithmetic mean	172	172	172
standard deviation	± 9	± 8	± 9
Weight Units: kg			
arithmetic mean	83	82	80
standard deviation	± 16	± 15	± 15
BMI			
Body Mass Index			
Units: kg/squaremeter			
arithmetic mean	27.7	27.4	26.8
standard deviation	± 4.3	± 4.1	± 3.9
Bupivacaine, SA			
Bupivacaine dose for spinal anesthesia (SA)			
Units: mg			
arithmetic mean	12	12	12
standard deviation	± 2	± 2	± 2
Sufentanil used if general anesthesia			
Sufentanil dose prior to end of surgery			
Units: micorgram			
arithmetic mean	24	20	21
standard deviation	± 7	± 9	± 8
Duration of surgery			

Units: minute			
arithmetic mean	54	51	53
standard deviation	± 19	± 14	± 18

Reporting group values	Treatment D	Total	
Number of subjects	139	556	
Age categorical			
Units: Subjects			
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	66		
standard deviation	± 10	-	
Gender categorical			
Units: Subjects			
Female	76	277	
Male	63	279	
ASA-score			
American Society of Anaesthesiologists Physical Status Classification System			
Units: Subjects			
ASA 1	43	165	
ASA 2	84	335	
ASA 3	12	56	
Anesthesia			
Type of Anesthesia			
Units: Subjects			
Spinal with sedation	69	270	
Spinal	27	151	
General	38	111	
Conversion of spinal to general	5	24	
Prior use of paracetamol			
Use of paracetamol prior to the operation.			
Units: Subjects			
No use	51	207	
As needed	22	99	
Daily use	66	250	
Prior use of NSAID			
Use of NSAID prior to the operation.			
Units: Subjects			
No use	72	295	
As needed	21	76	
Daily use	46	185	
Prior use of codeine			
Use of codeine prior to the operation			
Units: Subjects			
No use	137	548	
As needed	1	3	
Daily use	1	5	
Prior use of tramadol			

Use of tramadol prior to the operation.			
Units: Subjects			
No use	122	495	
As needed	8	25	
Daily use	9	36	
Type of surgery Units: Subjects			
No cement	122	500	
Cement	4	11	
Hybrid	13	45	
Height Units: cm			
arithmetic mean	171		
standard deviation	± 9	-	
Weight Units: kg			
arithmetic mean	81		
standard deviation	± 16	-	
BMI			
Body Mass Index			
Units: kg/squaremeter			
arithmetic mean	27.6		
standard deviation	± 4.7	-	
Bupivacaine, SA			
Bupivacaine dose for spinal anesthesia (SA)			
Units: mg			
arithmetic mean	12		
standard deviation	± 2	-	
Sufentanil used if general anesthesia			
Sufentanil dose prior to end of surgery			
Units: micorgram			
arithmetic mean	21		
standard deviation	± 8	-	
Duration of surgery Units: minute			
arithmetic mean	53		
standard deviation	± 15	-	

End points

End points reporting groups

Reporting group title	Treatment A
Reporting group description:	
Paracetamol 1g + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment B
Reporting group description:	
Paracetamol 1g + placebo orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment C
Reporting group description:	
Placebo + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment D
Reporting group description:	
Paracetamol 0,5 g + ibuprofen 200 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	

Primary: Morphine consumption the first 24 hours postoperatively

End point title	Morphine consumption the first 24 hours postoperatively
End point description:	
Total need for morphine administered as BOTH patient controlled analgesia (PCA) for the first 24 hours postoperatively AND supplemental morphine administered at the post-anaesthesia unit the first hour postoperatively. Bolus 2.0 mg; lockout: 10 min	
End point type	Primary
End point timeframe:	
0-24 hours postoperatively	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: miligram				
median (confidence interval 99.6%)	20 (0 to 148)	36 (0 to 166)	26 (2 to 139)	28 (2 to 145)

Statistical analyses

Statistical analysis title	Comparison of 24.hour morphine consumption, A vs B
Statistical analysis description:	
Pair-wise comparison of the groups.	
Comparison groups	Treatment A v Treatment B

Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Van Elteren
Parameter estimate	Median difference (final values)
Point estimate	-16
Confidence interval	
level	Other: 99.6 %
sides	2-sided
lower limit	-24
upper limit	-6.5

Notes:

[1] - P-value for this anlysis is corrected for co-primary outcome and 6 possible comparisons. P=0.0042.

Statistical analysis title	Comparison of 24.hour morphine consumption, A vs C
Statistical analysis description:	
Pair-wise comparison of the groups.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [2]
Method	Van Elteren
Parameter estimate	Median difference (final values)
Point estimate	-6
Confidence interval	
level	Other: 99.6 %
sides	2-sided
lower limit	-16
upper limit	-2

Notes:

[2] - P-value for this anlysis is corrected for co-primary outcome and 6 possible comparisons. P=0.0042.

Statistical analysis title	Comparison of 24.hour morphine consumption, A vs D
Statistical analysis description:	
Pair-wise comparison of the groups.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [3]
Method	Van Elteren
Parameter estimate	Median difference (final values)
Point estimate	-8
Confidence interval	
level	Other: 99.6 %
sides	2-sided
lower limit	-16
upper limit	2

Notes:
[3] - P-value for this anlysis is corrected for co-primary outcome and 6 possible comparisons. P=0.0042.

Statistical analysis title	Comparison of 24.hour morphine consumption,B vs C
Statistical analysis description:	
Pair-wise comparison of the groups.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044 [4]
Method	Van Elteren
Parameter estimate	Median difference (final values)
Point estimate	10
Confidence interval	
level	Other: 99.6 %
sides	2-sided
lower limit	-2
upper limit	16

Notes:
[4] - P-value for this anlysis is corrected for co-primary outcome and 6 possible comparisons. P=0.0042.

Statistical analysis title	Comparison of 24.hour morphine consumption,B vs D
Statistical analysis description:	
Pair-wise comparison of the groups.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [5]
Method	Van Elteren
Parameter estimate	Median difference (final values)
Point estimate	8
Confidence interval	
level	Other: 99.6 %
sides	2-sided
lower limit	-1
upper limit	14

Notes:
[5] - P-value for this anlysis is corrected for co-primary outcome and 6 possible comparisons. P=0.0042.

Statistical analysis title	Comparison of 24.hour morphine consumption, C vs D
Statistical analysis description:	
Pair-wise comparison of the groups.	
Comparison groups	Treatment D v Treatment C

Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [6]
Method	Van Elteren
Parameter estimate	Median difference (final values)
Point estimate	-2
Confidence interval	
level	Other: 99.6 %
sides	2-sided
lower limit	-7
upper limit	10

Notes:

[6] - P-value for this anlysis is corrected for co-primary outcome and 6 possible comparisons. P=0.0042.

Primary: Proportion of patients with 1 or more modified SAEs from the surgery to 90 days postoperatively

End point title	Proportion of patients with 1 or more modified SAEs from the surgery to 90 days postoperatively

End point description:

End point type	Primary

End point timeframe:

Surgery to 90 days postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	142	139	139
Units: Number of SAE	20	15	20	18

Statistical analyses

Statistical analysis title	Comparsion of porpotions of SAE

Statistical analysis description:

To investigate harm of ibuprofen, patients in the 3 groups randomized to receive ibuprofen (Treatment A + C + D) were compared with patients in the paracetamol-alone group (Treatment B) for the modified SAE outcome.

Comparison groups	Treatment A v Treatment B v Treatment C v Treatment D
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [7]
Method	Generalized estimating equations
Parameter estimate	Risk ratio (RR)
Point estimate	1.44

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.79
upper limit	2.64

Notes:

[7] - P-value is corrected for co-primary outcome. P=0.025.

Statistical analysis title	Proportions of modified SAEs

Statistical analysis description:

Proportion of patients with 1 or more modified SAEs from the surgery to 90 days postoperatively. To investigate harm of ibuprofen, patients in the 3 groups randomized to receive ibuprofen were compared with patients in the paracetamol-alone group for the modified SAE outcome.
A + C + D vs B

Comparison groups	Treatment A v Treatment B v Treatment C v Treatment D
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [8]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.44
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.79
upper limit	2.64

Notes:

[8] - Level of significance corrected, due to co-primary outcome to p= 0.025

Secondary: Pain scores, with mobilization at 6 h

End point title	Pain scores, with mobilization at 6 h

End point description:

End point type	Secondary

End point timeframe:

6 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: mm				
arithmetic mean (confidence interval 99.2%)	45 (39 to 51)	52 (47 to 58)	50 (44 to 55)	53 (48 to 58)

Statistical analyses

Statistical analysis title	Comparison pain scores 6 h, mob, A vs B
Statistical analysis description:	
Comparison of the pain scores 6 hours postoperatively, with mobilization.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [9]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-7
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-15
upper limit	1

Notes:

[9] - The statistically significance level i corrected for multiple comparisons til p=0.0084

Statistical analysis title	Comparison pain scores 6 h, mob, A vs D
Statistical analysis description:	
Comparison of the pain scores 6 hours postoperatively, with mobilization.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [10]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-8
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-15
upper limit	0

Notes:

[10] - The statistically significance level i corrected for multiple comparisons til p=0.0084

Statistical analysis title	Comparison pain scores 6 h, mob, B vs C
Statistical analysis description:	
Comparison of the pain scores 6 hours postoperatively, with mobilization.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34 [11]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	3

Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-5
upper limit	11

Notes:

[11] - The statistically significance level i corrected for multiple comparisons til p=0.0084

Statistical analysis title	Comparison pain scores 6 h, mob, B vs D

Statistical analysis description:

Comparison of the pain scores 6 hours postoperatively, with mobilization.

Comparison groups	Treatment D v Treatment B
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [12]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-8
upper limit	7

Notes:

[12] - The statistically significance level i corrected for multiple comparisons til p=0.0084

Statistical analysis title	Comparison pain scores 6 h, mob, C vs D

Statistical analysis description:

Comparison of the pain scores 6 hours postoperatively, with mobilization.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23 [13]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-3
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-11
upper limit	4

Notes:

[13] - The statistically significance level i corrected for multiple comparisons til p=0.0084

Statistical analysis title	Comparison pain scores 6 h, mob, A vs C

Statistical analysis description:

Comparison of the pain scores 6 hours postoperatively, with mobilization.

Comparison groups	Treatment A v Treatment C

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17 [14]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-12
upper limit	4

Notes:

[14] - The statistically significance level i corrected for multiple comparisons til p=0.0084

Secondary: Pain scores, at rest 6 hours

End point title	Pain scores, at rest 6 hours

End point description:

End point type	Secondary

End point timeframe:

6 hours postoperatively

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: mm				
arithmetic mean (confidence interval 99.2%)	32 (27 to 37)	39 (34 to 44)	37 (32 to 42)	36 (31 to 41)

Statistical analyses

Statistical analysis title	Comparison of pain scores, at rest 6 hours, A vs B

Statistical analysis description:

Comparison of pain scores, 6 hours postoperatively at rest.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [15]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-8

Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-15
upper limit	0

Notes:

[15] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 6 hours, A vs C

Statistical analysis description:

Comparison of pain scores, 6 hours postoperatively at rest.

Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [16]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-5
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-12
upper limit	2

Notes:

[16] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 6 hours, A vs D

Statistical analysis description:

Comparison of pain scores, 6 hours postoperatively at rest.

Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08 [17]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-5
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-11
upper limit	2

Notes:

[17] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 6 hours, B vs C

Statistical analysis description:

Comparison of pain scores, 6 hours postoperatively at rest.

Comparison groups	Treatment B v Treatment C

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 [18]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	2
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-5
upper limit	10

Notes:

[18] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 6 hours, B vs D
Statistical analysis description:	
Comparison of pain scores, 6 hours postoperatively at rest.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [19]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-4
upper limit	10

Notes:

[19] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 6 hours, C vs D
Statistical analysis description:	
Comparison of pain scores, 6 hours postoperatively at rest.	
Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [20]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-6
upper limit	8

Notes:
[20] - Statistical significance level corrected for multiple comparison to p=0.0084.

Secondary: Pain scores with mobilization at 24 hours

End point title	Pain scores with mobilization at 24 hours

End point description:

End point type	Secondary

End point timeframe:
24 hours postoperatively

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: mm				
arithmetic mean (confidence interval 99.2%)	37 (32 to 43)	49 (43 to 54)	45 (39 to 51)	46 (40 to 51)

Statistical analyses

Statistical analysis title	Comparison of pain scores, with mob 24 h, A vs B

Statistical analysis description:
Comparison of pain scores with mobilization 24 hours postoperatively.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [21]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-11
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-19
upper limit	-3

Notes:
[21] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, with mob 24 h, A vs C

Statistical analysis description:
Comparison of pain scores with mobilization 24 hours postoperatively.

Comparison groups	Treatment A v Treatment C

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [22]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-8
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-15
upper limit	0

Notes:

[22] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, with mob 24 h, A vs D
Statistical analysis description:	
Comparison of pain scores with mobilization 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [23]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-8
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-16
upper limit	0

Notes:

[23] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, with mob 24 h, B vs C
Statistical analysis description:	
Comparison of pain scores with mobilization 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [24]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	4
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-4
upper limit	12

Notes:
[24] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, with mob 24 h, B vs D
Statistical analysis description: Comparison of pain scores with mobilization 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 [25]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-5
upper limit	11

Notes:
[25] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, with mob 24 h, C vs D
Statistical analysis description: Comparison of pain scores with mobilization 24 hours postoperatively.	
Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [26]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-8
upper limit	7

Notes:
[26] - Statistical significance level corrected for multiple comparison to p=0.0084.

Secondary: Pain scores at rest at 24 hours

End point title	Pain scores at rest at 24 hours
End point description:	

End point type	Secondary
End point timeframe: 24 hours postoperatively.	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: mm				
arithmetic mean (confidence interval 99.2%)	13 (10 to 17)	24 (19 to 29)	21 (16 to 26)	19 (15 to 23)

Statistical analyses

Statistical analysis title	Comparison of pain scores, at rest 24 h, A vs B
Statistical analysis description: Comparison of pain scores at rest 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [27]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-11
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-17
upper limit	-5

Notes:
[27] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 24 h, A vs C
Statistical analysis description: Comparison of pain scores at rest 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [28]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-8
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-13
upper limit	-2

Notes:
[28] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 24 h, A vs D
Statistical analysis description: Comparison of pain scores at rest 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [29]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	-6
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-11
upper limit	0

Notes:
[29] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 24 h, B vs C
Statistical analysis description: Comparison of pain scores at rest 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 [30]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-4
upper limit	10

Notes:
[30] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 24 h, B vs D
Statistical analysis description: Comparison of pain scores at rest 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [31]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	5
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-2
upper limit	11

Notes:

[31] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of pain scores, at rest 24 h, C vs D

Statistical analysis description:

Comparison of pain scores at rest 24 hours postoperatively.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [32]
Method	Generalized estimating equation (GEE)
Parameter estimate	Mean difference (final values)
Point estimate	2
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	-4
upper limit	8

Notes:

[32] - Statistical significance level corrected for multiple comparison to p=0.0084.

Secondary: Adverse events in the first 24 h

End point title	Adverse events in the first 24 h

End point description:

End point type	Secondary

End point timeframe:

The first 24 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: Adverse events	20	23	22	21

Statistical analyses

Statistical analysis title	Comparison of AE in the first 24 hours, A vs B
Statistical analysis description:	
Mean difference (RR) of adverse events in the first 24 hours.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73 [33]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.91
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.43
upper limit	1.91

Notes:

[33] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of AE in the first 24 hours, A vs C
Statistical analysis description:	
Mean difference (RR) of adverse events in the first 24 hours.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [34]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.44
upper limit	1.98

Notes:

[34] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of AE in the first 24 hours, A vs D
Statistical analysis description:	
Mean difference (RR) of adverse events in the first 24 hours.	

Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [35]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.02
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.47
upper limit	2.22

Notes:

[35] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of AE in the first 24 hours, B vs C

Statistical analysis description:

Mean difference (RR) of adverse events in the first 24 hours.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93 [36]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.02
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.5
upper limit	2.11

Notes:

[36] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of AE in the first 24 hours, B vs D

Statistical analysis description:

Mean difference (RR) of adverse events in the first 24 hours.

Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 [37]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.13

Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.53
upper limit	2.37

Notes:

[37] - Statistical significance level corrected for multiple comparison to p=0.0084.

Statistical analysis title	Comparison of AE in the first 24 hours, C vs D

Statistical analysis description:

Mean difference (RR) of adverse events in the first 24 hours.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74 [38]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.1
Confidence interval	
level	Other: 99.2 %
sides	2-sided
lower limit	0.52
upper limit	2.34

Notes:

[38] - Statistical significance level corrected for multiple comparison to p=0.0084.

Other pre-specified: Nausea, 6 hours %

End point title	Nausea, 6 hours %

End point description:

End point type	Other pre-specified

End point timeframe:

Surgery to 24 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135	139	130	134
Units: mild, moderat, severe nausea	22	32	19	28

Statistical analyses

Statistical analysis title	Comparison nausea 6 hours, A vs B

Statistical analysis description:

Comparison of the proportions of nausea 6 hours postoperatively.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17 [39]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.15

Notes:

[39] - Significance level p= 0.05

Statistical analysis title	Comparison nausea 6 hours, A vs C
Statistical analysis description:	
Comparison of the proportions of nausea 6 hours postoperatively.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82 [40]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.86

Notes:

[40] - Significance level p= 0.05

Statistical analysis title	Comparison nausea 6 hours, A vs D
Statistical analysis description:	
Comparison of the proportions of nausea 6 hours postoperatively.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [41]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.29

Notes:

[41] - Significance level p= 0.05

Statistical analysis title	Comparison nausea 6 hours, B vs C

Statistical analysis description:

Comparison of the proportions of nausea 6 hours postoperatively.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11 [42]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.5

Notes:

[42] - Significance level p= 0.05

Statistical analysis title	Comparison nausea 6 hours, B vs D

Statistical analysis description:

Comparison of the proportions of nausea 6 hours postoperatively.

Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 [43]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.72

Notes:

[43] - Significance level p= 0.05

Statistical analysis title	Comparison nausea 6 hours, C vs D

Statistical analysis description:

Comparison of the proportions of nausea 6 hours postoperatively.

Comparison groups	Treatment D v Treatment C

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [44]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.23

Notes:
[44] - Significance level p= 0.05

Other pre-specified: Nausea, 24 hours postoperatively

End point title	Nausea, 24 hours postoperatively

End point description:

End point type	Other pre-specified

End point timeframe:
24 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134	137	132	135
Units: mild, moderate, severe nausea	17	33	30	38

Statistical analyses

Statistical analysis title	Comparison nausea 24 hours, A vs B

Statistical analysis description:
Comparison of proportions of nausea at 24 hours postoperatively.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [45]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.9

Notes:

[45] - Level of significance p = 0.05.

Statistical analysis title	Comparison nausea 24 hours, A vs C

Statistical analysis description:

Comparison of proportions of nausea at 24 hours postoperatively.

Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036 [46]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.96

Notes:

[46] - Level of significance p = 0.05.

Statistical analysis title	Comparison nausea 24 hours, A vs D

Statistical analysis description:

Comparison of proportions of nausea at 24 hours postoperatively.

Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [47]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.76

Notes:

[47] - Level of significance p = 0.05.

Statistical analysis title	Comparison nausea 24 hours, B vs C

Statistical analysis description:

Comparison of proportions of nausea at 24 hours postoperatively.

Comparison groups	Treatment B v Treatment C

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [48]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.63

Notes:

[48] - Level of significance p = 0.05.

Statistical analysis title	Comparison nausea 24 hours, B vs D
Statistical analysis description:	
Comparison of proportions of nausea at 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45 [49]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.28

Notes:

[49] - Level of significance p = 0.05.

Statistical analysis title	Comparison nausea 24 hours, C vs D
Statistical analysis description:	
Comparison of proportions of nausea at 24 hours postoperatively.	
Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [50]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.22

Notes:
[50] - Level of significance p = 0.05.

Other pre-specified: Sedation 6 hours postoperatively

End point title	Sedation 6 hours postoperatively

End point description:

End point type	Other pre-specified

End point timeframe:
6 hours postoperatively

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135	138	130	132
Units: mild, moderate, severe sedation	33	51	27	38

Statistical analyses

Statistical analysis title	Comparison sedation 6 hours, A vs B

Statistical analysis description:
Comparison of proportions of sedation 6 hours postoperatively.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [51]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.96

Notes:
[51] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 6 hours, A vs C

Statistical analysis description:
Comparison of proportions of sedation 6 hours postoperatively.

Comparison groups	Treatment A v Treatment C

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48 [52]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.84

Notes:

[52] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 6 hours, A vs D
Statistical analysis description:	
Comparison of proportions of sedation 6 hours postoperatively.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42 [53]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.27

Notes:

[53] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 6 hours, B vs C
Statistical analysis description:	
Comparison of proportions of sedation 6 hours postoperatively.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [54]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	2.66

Notes:
[54] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 6 hours, B vs D
Statistical analysis description: Comparison of proportions of sedation 6 hours postoperatively.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16 [55]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.81

Notes:
[55] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 6 hours, C vs D
Statistical analysis description: Comparison of proportions of sedation 6 hours postoperatively.	
Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [56]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.11

Notes:
[56] - Level of significance p = 0.05

Other pre-specified: Sedation, 24 hours postoperatively	
End point title	Sedation, 24 hours postoperatively
End point description:	
End point type	Other pre-specified
End point timeframe: 24 hours postoperatively.	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134	137	132	135
Units: mild, moderate, severe sedation	44	58	47	57

Statistical analyses

Statistical analysis title	Comparison sedation 24 hours, A vs B
Statistical analysis description: Comaprison of proportions of sedation 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [57]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.9

Notes:
[57] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 24 hours, A vs C
Statistical analysis description: Comaprison of proportions of sedation 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036 [58]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.96

Notes:
[58] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 24 hours, A vs D
Statistical analysis description:	
Comaprison of proportions of sedation 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [59]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.76

Notes:
[59] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 24 hours, B vs C
Statistical analysis description:	
Comaprison of proportions of sedation 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [60]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.63

Notes:
[60] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 24 hours, B vs D
Statistical analysis description:	
Comaprison of proportions of sedation 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45 [61]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.28

Notes:

[61] - Level of significance p = 0.05

Statistical analysis title	Comparison sedation 24 hours, C vs D

Statistical analysis description:

Comaprison of proportions of sedation 24 hours postoperatively.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [62]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.22

Notes:

[62] - Level of significance p = 0.05

Other pre-specified: Dizziness, 6 hours postoperatively

End point title	Dizziness, 6 hours postoperatively

End point description:

End point type	Other pre-specified

End point timeframe:

6 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135	139	130	133
Units: mild, moderate, severe dizziness	19	35	26	32

Statistical analyses

Statistical analysis title	Comparison dizziness 6 hours, A vs B
Statistical analysis description: Comparison of proportions of dizziness 6 hours postoperatively.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [63]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.93

Notes:
[63] - Level of significance p = 0.05

Statistical analysis title	Comparison dizziness 6 hours, A vs C
Statistical analysis description: Comparison of proportions of dizziness 6 hours postoperatively.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [64]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.21

Notes:
[64] - Level of significance p = 0.05

Statistical analysis title	Comparison dizziness 6 hours, A vs D
Statistical analysis description: Comparison of proportions of dizziness 6 hours postoperatively.	

Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [65]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.98

Notes:

[65] - Level of significance p = 0.05

Statistical analysis title	Comparison dizziness 6 hours, B vs C

Statistical analysis description:

Comparison of proportions of dizziness 6 hours postoperatively.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [66]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.97

Notes:

[66] - Level of significance p = 0.05

Statistical analysis title	Comparison dizziness 6 hours, B vs D

Statistical analysis description:

Comparison of proportions of dizziness 6 hours postoperatively.

Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83 [67]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.59

Notes:
[67] - Level of significance p = 0.05

Statistical analysis title	Comparison dizziness 6 hours, C vs D

Statistical analysis description:
Comparison of proportions of dizziness 6 hours postoperatively.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43 [68]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.31

Notes:
[68] - Level of significance p = 0.05

Other pre-specified: Dizziness, 24 hours postoperatively

End point title	Dizziness, 24 hours postoperatively

End point description:

End point type	Other pre-specified

End point timeframe:
24 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134	137	132	135
Units: mild, moderate, severe dizziness	26	32	38	37

Statistical analyses

Statistical analysis title	Comparison dizziness 24 hours, A vs B

Statistical analysis description:
Comparison of proportions of dizziness 24 hours postoperatively.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43 [69]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.32

Notes:

[69] - Level of significance p = 0.05.

Statistical analysis title	Comparison dizziness 24 hours, A vs C

Statistical analysis description:

Comparison of proportions of dizziness 24 hours postoperatively.

Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77 [70]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.04

Notes:

[70] - Level of significance p = 0.05.

Statistical analysis title	Comparison dizziness 24 hours, A vs D

Statistical analysis description:

Comparison of proportions of dizziness 24 hours postoperatively.

Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [71]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.1

Notes:

[71] - Level of significance p = 0.05.

Statistical analysis title	Comparison dizziness 24 hours, B vs C
Statistical analysis description:	
Comparison of proportions of dizziness 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [72]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.22

Notes:

[72] - Level of significance p = 0.05.

Statistical analysis title	Comparison dizziness 24 hours, B vs D
Statistical analysis description:	
Comparison of proportions of dizziness 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 [73]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.28

Notes:

[73] - Level of significance p = 0.05.

Statistical analysis title	Copy of Comparison dizziness 24 hours, C vs D
Statistical analysis description:	
Comparison of proportions of dizziness 24 hours postoperatively.	
Comparison groups	Treatment D v Treatment C

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [74]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.54

Notes:

[74] - Level of significance p = 0.05.

Other pre-specified: Vomiting, first 24 hours postoperatively.

End point title	Vomiting, first 24 hours postoperatively.

End point description:

End point type	Other pre-specified

End point timeframe:

First 24 hours postoperatively.

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	141	137	137
Units: number of vomiting	0	0	0	0

Statistical analyses

Statistical analysis title	Comparison of vomiting, first 24 hours, A vs B

Statistical analysis description:

Comparison of vomiting, the first 24 hours postoperatively.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Comparison of vomiting, first 24 hours, A vs C
Statistical analysis description:	
Comparison of vomiting, the first 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Comparison of vomiting, first 24 hours, A vs D
Statistical analysis description:	
Comparison of vomiting, the first 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Statistical analysis title	Comparison of vomiting, first 24 hours, B vs C
Statistical analysis description:	
Comparison of vomiting, the first 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment C

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Statistical analysis title	Comparison of vomiting, first 24 hours, B vs D
Statistical analysis description: Comparison of vomiting, the first 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Statistical analysis title	Comparison of vomiting, first 24 hours, C vs D
Statistical analysis description: Comparison of vomiting, the first 24 hours postoperatively.	
Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Other pre-specified: Ondansetron use first 24 hours	
End point title	Ondansetron use first 24 hours
End point description:	
End point type	Other pre-specified
End point timeframe:	
First 24 hours postoperatively.	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	140	136	139
Units: mg				
median (inter-quartile range (Q1-Q3))	0 (0 to 4)	0 (0 to 4)	0 (0 to 4)	0 (0 to 5)

Statistical analyses

Statistical analysis title	Comparsion of ondansetron use, first 24 h, A vs B
Statistical analysis description:	
Comparison of the use of ondansetron, the first 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [75]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0

Notes:

[75] - Level of significance p = 0.05

Statistical analysis title	Comparsion of ondansetron use, first 24 h, A vs C
Statistical analysis description:	
Comparison of the use of ondansetron, the first 24 hours postoperatively.	
Comparison groups	Treatment A v Treatment C

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [76]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[76] - Level of significance p = 0.05

Statistical analysis title	Comparsion of ondansetron use, first 24 h, A vs D
Statistical analysis description:	
Comparison of the use of ondansetron, the first 24 hours postoperatively.	
Comparison groups	Treatment D v Treatment A
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [77]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Notes:

[77] - Level of significance p = 0.05

Statistical analysis title	Comparsion of ondansetron use, first 24 h, B vs C
Statistical analysis description:	
Comparison of the use of ondansetron, the first 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15 [78]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2

Notes:
[78] - Level of significance p = 0.05

Statistical analysis title	Comparsion of ondansetron use, first 24 h, B vs D
Statistical analysis description: Comparison of the use of ondansetron, the first 24 hours postoperatively.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73 [79]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	2

Notes:
[79] - Level of significance p = 0.05

Statistical analysis title	Comparsion of ondansetron use, first 24 h, C vs D
Statistical analysis description: Comparison of the use of ondansetron, the first 24 hours postoperatively.	
Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [80]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0

Notes:
[80] - Level of significance p = 0.05

Other pre-specified: Blood loss	
End point title	Blood loss
End point description: Exploratory outcome	
End point type	Other pre-specified
End point timeframe: Peroperative blood loss.	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132	137	136	134
Units: ml				
median (inter-quartile range (Q1-Q3))	300 (200 to 415)	300 (200 to 470)	265 (177.5 to 400)	287.5 (165 to 400)

Statistical analyses

Statistical analysis title	Comparison blood loss, A vs B
Statistical analysis description: Comparsion of peroperative blood loss in ml.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9 [81]
Method	Generalized estimating equation (GEE)
Parameter estimate	Risk ratio (RR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60
upper limit	52.5

Notes:
[81] - Level of Significance p = 0.05

Statistical analysis title	Comparison blood loss, A vs C
Statistical analysis description: Comparsion of peroperative blood loss in ml.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29 [82]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25
upper limit	85

Notes:
[82] - Level of Significance p = 0.05

Statistical analysis title	Comparison blood loss, A vs D
Statistical analysis description: Comparsion of peroperative blood loss in ml.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36 [83]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50
upper limit	65

Notes:
[83] - Level of Significance p = 0.05

Statistical analysis title	Comparison blood loss, B vs C
Statistical analysis description: Comparsion of peroperative blood loss in ml.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19 [84]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	100

Notes:
[84] - Level of Significance p = 0.05

Statistical analysis title	Comparison blood loss, B vs D
Statistical analysis description: Comparsion of peroperative blood loss in ml.	
Comparison groups	Treatment B v Treatment D

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37 [85]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50
upper limit	50

Notes:

[85] - Level of Significance p = 0.05

Statistical analysis title	Comparison blood loss,v C vs D

Statistical analysis description:

Comparsion of peroperative blood loss in ml.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85 [86]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	-22.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75
upper limit	50

Notes:

[86] - Level of Significance p = 0.05

Other pre-specified: Days alive and outside hospital, days

End point title	Days alive and outside hospital, days

End point description:

Exploratory outcome

End point type	Other pre-specified

End point timeframe:

Days alive and outside hospital, days

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	134	141	138	138
Units: days				
median (inter-quartile range (Q1-Q3))	89 (88 to 89)	88 (88 to 89)	88 (88 to 89)	88 (88 to 89)

Statistical analyses

Statistical analysis title	Median differences, days alive and outside, A vs B
Statistical analysis description:	
Median differences of days alive and outside of hospital.	
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [87]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[87] - Level of significance p = 0.05.

Statistical analysis title	Median differences, days alive and outside, A vs C
Statistical analysis description:	
Median differences of days alive and outside of hospital.	
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [88]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[88] - Level of significance p = 0.05.

Statistical analysis title	Median differences, days alive and outside, A vs D

Statistical analysis description:	
Median differences of days alive and outside of hospital.	
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55 [89]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Notes:

[89] - Level of significance p = 0.05.

Statistical analysis title	Median differences, days alive and outside, B vs C
Statistical analysis description:	
Median differences of days alive and outside of hospital.	
Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69 [90]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	2

Notes:

[90] - Level of significance p = 0.05.

Statistical analysis title	Median differences, days alive and outside, B vs D
Statistical analysis description:	
Median differences of days alive and outside of hospital.	
Comparison groups	Treatment B v Treatment D
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [91]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[91] - Level of significance p = 0.05.

Statistical analysis title	Median differences, days alive and outside, C vs D

Statistical analysis description:

Median differences of days alive and outside of hospital.

Comparison groups	Treatment D v Treatment C
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56 [92]
Method	Generalized estimating equation (GEE)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1

Notes:

[92] - Level of significance p = 0.05.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From operation to 90 days postoperatively.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICH-GCP
Dictionary version	Revision 2

Reporting groups	
Reporting group title	Treatment A
Reporting group description: Paracetamol 1g + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment B
Reporting group description: Paracetamol 1g + placebo orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment C
Reporting group description: Placebo + ibuprofen 400 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	
Reporting group title	Treatment D
Reporting group description: Paracetamol 0,5 g + ibuprofen 200 mg orally starting 1 hour before surgery and given with 6-hour intervals (+/- 1 hour) i.e. a total of 4 times the first 24 hours postoperative.	

Serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 136 (18.38%)	15 / 142 (10.56%)	20 / 139 (14.39%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Unknown			
subjects affected / exposed	5 / 136 (3.68%)	4 / 142 (2.82%)	3 / 139 (2.16%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep venous thrombosis (CVT)			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 136 (0.74%)	1 / 142 (0.70%)	0 / 139 (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
Surgical and medical procedures			
Mechanical problems with the prosthesis			
subjects affected / exposed	5 / 136 (3.68%)	4 / 142 (2.82%)	3 / 139 (2.16%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiological			
subjects affected / exposed	1 / 136 (0.74%)	1 / 142 (0.70%)	3 / 139 (2.16%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Delirium			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Low hemoglobin			
subjects affected / exposed	2 / 136 (1.47%)	0 / 142 (0.00%)	0 / 139 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dyspepsia			

subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	0 / 139 (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
Constipation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	0 / 139 (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			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	0 / 139 (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			
Fracture, not anatomical related			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Surgical site infection			
subjects affected / exposed	5 / 136 (3.68%)	4 / 142 (2.82%)	5 / 139 (3.60%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection, not anatomical related			

subjects affected / exposed	1 / 136 (0.74%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment D		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 139 (12.95%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Unknown			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep venous thrombosis (CVT)			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Mechanical problems with the prosthesis			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiological			
subjects affected / exposed	3 / 139 (2.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Delirium			

subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Low hemoglobin			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			

subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture, not anatomical related			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Surgical site infection			
subjects affected / exposed	4 / 139 (2.88%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Infection, not anatomical related			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 136 (14.71%)	23 / 142 (16.20%)	22 / 139 (15.83%)
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	0	0	0
Low blood pressure			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	3 / 139 (2.16%)
occurrences (all)	0	0	3

Surgical and medical procedures			
Hot flush when using PCA-morphine			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences (all)	0	0	2
Leaking from surgical site			
subjects affected / exposed	0 / 136 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences (all)	0	1	1
Transfer to an other hospital			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences (all)	0	0	1
Vasovagal episode during anesthesia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Confusion			
subjects affected / exposed	2 / 136 (1.47%)	3 / 142 (2.11%)	4 / 139 (2.88%)
occurrences (all)	2	3	4
Headache			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	1 / 136 (0.74%)	2 / 142 (1.41%)	1 / 139 (0.72%)
occurrences (all)	1	2	1
Vasovagal episode during mobilization			
subjects affected / exposed	1 / 136 (0.74%)	3 / 142 (2.11%)	1 / 139 (0.72%)
occurrences (all)	1	3	1
Blood and lymphatic system disorders			
Low hemoglobin			
subjects affected / exposed	3 / 136 (2.21%)	0 / 142 (0.00%)	2 / 139 (1.44%)
occurrences (all)	3	0	2
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	3 / 136 (2.21%)	4 / 142 (2.82%)	1 / 139 (0.72%)
occurrences (all)	3	4	1
Incontinence (stool)			

subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 136 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	0	1	0
Ructus			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 136 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Itching, PCA			
subjects affected / exposed	7 / 136 (5.15%)	5 / 142 (3.52%)	3 / 139 (2.16%)
occurrences (all)	7	5	3
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	1	0	0
Elevated creatinin			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	1 / 139 (0.72%)
occurrences (all)	0	0	1
Endocrine disorders			
Low potassium			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Fall			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	1	0	0
Not mobilized			
subjects affected / exposed	0 / 136 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	0	1	0
Shivering			
subjects affected / exposed	0 / 136 (0.00%)	1 / 142 (0.70%)	0 / 139 (0.00%)
occurrences (all)	0	1	0

Syncope during mobilization			
subjects affected / exposed	1 / 136 (0.74%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Fever			
subjects affected / exposed	0 / 136 (0.00%)	1 / 142 (0.70%)	1 / 139 (0.72%)
occurrences (all)	0	1	1
Product issues			
Pain when using PCA-morphine			
subjects affected / exposed	0 / 136 (0.00%)	0 / 142 (0.00%)	0 / 139 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Treatment D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 139 (15.11%)		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Low blood pressure			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Hot flush when using PCA-morphine			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Leaking from surgical site			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences (all)	0		
Transfer to an other hospital			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences (all)	0		
Vasovagal episode during anesthesia			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Nervous system disorders			
Confusion			

subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences (all)	0		
Vasovagal episode during mobilization			
subjects affected / exposed	0 / 139 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Low hemoglobin			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences (all)	2		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	5 / 139 (3.60%)		
occurrences (all)	5		
Incontinence (stool)			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Ructus			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 139 (0.72%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Itching, PCA			
subjects affected / exposed	2 / 139 (1.44%)		
occurrences (all)	2		
Renal and urinary disorders			

Hematuria subjects affected / exposed occurrences (all) Elevated creatinin subjects affected / exposed occurrences (all)	0 / 139 (0.00%) 0 1 / 139 (0.72%) 1		
Endocrine disorders Low potassium subjects affected / exposed occurrences (all)	1 / 139 (0.72%) 1		
Musculoskeletal and connective tissue disorders Fall subjects affected / exposed occurrences (all) Not mobilized subjects affected / exposed occurrences (all) Shivering subjects affected / exposed occurrences (all) Syncope during mobilization subjects affected / exposed occurrences (all)	0 / 139 (0.00%) 0 1 / 139 (0.72%) 1 0 / 139 (0.00%) 0 0 / 139 (0.00%) 0		
Infections and infestations Fever subjects affected / exposed occurrences (all)	0 / 139 (0.00%) 0		
Product issues Pain when using PCA-morphine subjects affected / exposed occurrences (all)	1 / 139 (0.72%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30747964

http://www.ncbi.nlm.nih.gov/pubmed/31648374

http://www.ncbi.nlm.nih.gov/pubmed/32270482