



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy.

Summary

EudraCT number	2017-001636-19
Trial protocol	BE
Global end of trial date	29 January 2018

Results information

Result version number	v1 (current)
This version publication date	15 February 2019
First version publication date	15 February 2019

Trial information

Trial identification

Sponsor protocol code	HTX-011-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03237481
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Heron Therapeutics, Inc.
Sponsor organisation address	4242 Campus Point Ct #200, San Diego, United States, 92121
Public contact	HTX-011-302 Team, Heron Therapeutics, Inc., 001 858251 4405,
Scientific contact	HTX-011-302 Team, Heron Therapeutics, Inc., 001 858251 4405,

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	13 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2017
Global end of trial reached?	Yes
Global end of trial date	29 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral open inguinal herniorrhaphy.

Protection of trial subjects:

This study was conducted in compliance with the protocol and all applicable regulatory requirements in accordance with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and in general conformity with the most recent version of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	United States: 414
Worldwide total number of subjects	418
EEA total number of subjects	4

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)	387
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened within 28 days prior to surgery. Subjects who met the Screening eligibility criteria were randomized.

Period 1

Period 1 title	Overall Study (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Group 1

Arm description:

HTX-011, 2.5%/0.075% (bupivacaine/meloxicam doses), 10.3 mL, via instillation into the surgical site.

Arm type	Experimental
Investigational medicinal product name	HTX-011
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release solution for injection
Routes of administration	Local use

Dosage and administration details:

HTX-011, 2.5%/0.075% (bupivacaine/meloxicam doses), 10.3 mL, via instillation into the surgical site.

Arm title	Treatment Group 2
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Arm description:

Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site.

Arm type	Active comparator
Investigational medicinal product name	Bupivacaine hydrochloride, USP
Investigational medicinal product code	
Other name	Bupivacaine HCl
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site.

Arm title	Treatment Group 3
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Arm description:

Saline placebo, 10.3 mL, via instillation into the surgical site.

Arm type	Placebo
Investigational medicinal product name	Saline Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Local use

Dosage and administration details:

Saline placebo, 10.3 mL, via instillation into the surgical site.

Number of subjects in period 1	Treatment Group 1	Treatment Group 2	Treatment Group 3
Started	164	172	82
Completed	159	170	81
Not completed	5	2	1
Consent withdrawn by subject	3	2	1
Lost to follow-up	1	-	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment Group 1
Reporting group description: HTX-011, 2.5%/0.075% (bupivacaine/meloxicam doses), 10.3 mL, via instillation into the surgical site.	
Reporting group title	Treatment Group 2
Reporting group description: Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site.	
Reporting group title	Treatment Group 3
Reporting group description: Saline placebo, 10.3 mL, via instillation into the surgical site.	

Reporting group values	Treatment Group 1	Treatment Group 2	Treatment Group 3
Number of subjects	164	172	82
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	149	161	77
From 65-84 years	15	11	5
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	48.9	49.4	48.0
standard deviation	± 13.29	± 11.26	± 14.59
Gender categorical			
Units: Subjects			
Female	12	8	3
Male	152	164	79

Reporting group values	Total		
Number of subjects	418		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	387		

From 65-84 years	31		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	23		
Male	395		

End points

End points reporting groups

Reporting group title	Treatment Group 1
Reporting group description: HTX-011, 2.5%/0.075% (bupivacaine/meloxicam doses), 10.3 mL, via instillation into the surgical site.	
Reporting group title	Treatment Group 2
Reporting group description: Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site.	
Reporting group title	Treatment Group 3
Reporting group description: Saline placebo, 10.3 mL, via instillation into the surgical site.	

Primary: Mean AUC0-72 of the NRS-A pain intensity score for HTX-011 compared with saline placebo

End point title	Mean AUC0-72 of the NRS-A pain intensity score for HTX-011 compared with saline placebo ^[1]
End point description: Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) for HTX 011 compared with saline placebo.	
End point type	Primary
End point timeframe: 72 hours	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm excluded from this Endpoint reported in previous Endpoint.

End point values	Treatment Group 1	Treatment Group 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	82		
Units: NRS-A				
arithmetic mean (standard deviation)	269.39 (\pm 173.719)	350.82 (\pm 171.224)		

Statistical analyses

Statistical analysis title	HTX-011 vs Saline Placebo
Comparison groups	Treatment Group 1 v Treatment Group 3
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANOVA
Parameter estimate	Least Squares Mean Difference (LSMD)
Point estimate	-81.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	-125.83
upper limit	-37.02
Variability estimate	Standard error of the mean
Dispersion value	22.592

Secondary: Mean AUC0-72 of the NRS-A pain intensity score for HTX-011 compared with bupivacaine HCI

End point title	Mean AUC0-72 of the NRS-A pain intensity score for HTX-011 compared with bupivacaine HCI ^[2]
End point description: Mean AUC0-72 of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCI.	
End point type	Secondary
End point timeframe: 72 hours	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm excluded from this Endpoint reported in subsequent Endpoint.

End point values	Treatment Group 1	Treatment Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	82		
Units: NRS-A				
arithmetic mean (standard deviation)	269.39 (± 173.719)	341.88 (± 158.303)		

Statistical analyses

Statistical analysis title	HTX-011 vs. Bupivacaine HCI
Comparison groups	Treatment Group 2 v Treatment Group 1
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Least Squares Mean Difference (LSMD)
Point estimate	-72.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-108.32
upper limit	-36.65
Variability estimate	Standard error of the mean
Dispersion value	18.23

Secondary: Mean total postoperative opioid consumption for HTX-011 compared with saline placebo

End point title	Mean total postoperative opioid consumption for HTX-011 compared with saline placebo ^[3]
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End point description:

Mean total postoperative opioid consumption (in morphine equivalents) for HTX-011 compared with saline placebo.

End point type	Secondary
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End point timeframe:

72 hours

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arm excluded from this Endpoint reported in subsequent Endpoint.

End point values	Treatment Group 1	Treatment Group 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	82		
Units: Milligram morphine equivalents (MME)				
arithmetic mean (standard deviation)	10.85 (± 17.062)	17.53 (± 18.908)		

Statistical analyses

Statistical analysis title	HTX-011 vs. saline placebo
Comparison groups	Treatment Group 1 v Treatment Group 3
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl.

End point title	Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl. ^[4]
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End point description:

Proportion of subjects who are opioid-free for HTX-011 compared with bupivacaine HCl.

End point type	Secondary
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End point timeframe:

72 hours

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not Applicable

End point values	Treatment Group 1	Treatment Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	172		
Units: Subjects	84	69		

Statistical analyses

Statistical analysis title	HTX-011 vs. bupivacaine HCl
Comparison groups	Treatment Group 1 v Treatment Group 2
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0486
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.003
upper limit	0.218

Secondary: Mean total postoperative opioid consumption for HTX-011 compared with bupivacaine HCl

End point title	Mean total postoperative opioid consumption for HTX-011 compared with bupivacaine HCl ^[5]
End point description:	Mean total postoperative opioid consumption (in morphine equivalents) for HTX-011 compared with bupivacaine HCl.
End point type	Secondary
End point timeframe:	72 hours

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arm excluded from this Endpoint reported in subsequent Endpoint.

End point values	Treatment Group 1	Treatment Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	172		
Units: Milligram morphine equivalents (MME)				
arithmetic mean (standard deviation)	10.85 (\pm 17.062)	14.51 (\pm 18.185)		

Statistical analyses

Statistical analysis title	HTX-011 vs. bupivacaine HCl
Comparison groups	Treatment Group 1 v Treatment Group 2
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of Treatment-Emergent Adverse Events (TEAs)

End point title	Incidence of Treatment-Emergent Adverse Events (TEAs)
End point description:	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	172 ^[6]	82	
Units: Subjects reporting TEAs	119	127	61	

Notes:

[6] - One subject was randomized to HTX-011, but received bupivacaine HCl (Safety Population N=173).

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Serious Adverse Events (SAEs)

End point title	Incidence of Serious Adverse Events (SAEs)
End point description:	
End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	172 ^[7]	82	
Units: Subjects reporting SAEs	2	1	1	

Notes:

[7] - One subject was randomized to HTX-011, but received bupivacaine HCl (Safety Population N=173).

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Opioid-related Adverse Events (ORAEs)

End point title	Incidence of Opioid-related Adverse Events (ORAEs)
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End point description:

End point type	Secondary
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End point timeframe:

28 days

End point values	Treatment Group 1	Treatment Group 2	Treatment Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	172 ^[8]	82	
Units: Subjects reporting ORAEs	53	73	36	

Notes:

[8] - One subject was randomized to HTX-011, but received bupivacaine HCl (Safety Population N=173).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days

Adverse event reporting additional description:

For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Treatment Group 1
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Reporting group description:

HTX 011, HTX-011 2.5%/0.075% (bupivacaine/meloxicam doses), 10.3 mL, via instillation into the surgical site.

Reporting group title	Treatment Group 2
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Reporting group description:

Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site.

Reporting group title	Treatment Group 3
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Reporting group description:

Saline placebo, 10.3 mL, via instillation into the surgical site.

Serious adverse events	Treatment Group 1	Treatment Group 2	Treatment Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 163 (1.23%)	1 / 173 (0.58%)	1 / 82 (1.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 163 (0.00%)	1 / 173 (0.58%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 163 (0.00%)	0 / 173 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 163 (0.61%)	0 / 173 (0.00%)	0 / 82 (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
Infections and infestations			
Incision site haematoma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 173 (0.00%)	0 / 82 (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
Cellulitis of male external genital organ			
subjects affected / exposed	0 / 163 (0.00%)	0 / 173 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 163 (0.00%)	0 / 173 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Treatment Group 1	Treatment Group 2	Treatment Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 163 (73.01%)	127 / 173 (73.41%)	61 / 82 (74.39%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 163 (1.23%)	5 / 173 (2.89%)	6 / 82 (7.32%)
occurrences (all)	2	5	6
Cardiac disorders			
Bradycardia			
subjects affected / exposed	15 / 163 (9.20%)	16 / 173 (9.25%)	6 / 82 (7.32%)
occurrences (all)	15	16	6
Nervous system disorders			
Dizziness			

subjects affected / exposed occurrences (all)	24 / 163 (14.72%) 24	42 / 173 (24.28%) 42	13 / 82 (15.85%) 13
Headache subjects affected / exposed occurrences (all)	21 / 163 (12.88%) 21	24 / 173 (13.87%) 24	10 / 82 (12.20%) 10
Dysgeusia subjects affected / exposed occurrences (all)	15 / 163 (9.20%) 15	21 / 173 (12.14%) 21	3 / 82 (3.66%) 3
Tremor subjects affected / exposed occurrences (all)	7 / 163 (4.29%) 7	12 / 173 (6.94%) 12	8 / 82 (9.76%) 8
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	3 / 163 (1.84%) 3	6 / 173 (3.47%) 6	5 / 82 (6.10%) 5
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	30 / 163 (18.40%) 30	37 / 173 (21.39%) 37	28 / 82 (34.15%) 28
Constipation subjects affected / exposed occurrences (all)	28 / 163 (17.18%) 28	41 / 173 (23.70%) 41	15 / 82 (18.29%) 15
Vomiting subjects affected / exposed occurrences (all)	7 / 163 (4.29%) 7	12 / 173 (6.94%) 12	4 / 82 (4.88%) 4
Skin and subcutaneous tissue disorders Skin odour abnormal subjects affected / exposed occurrences (all)	13 / 163 (7.98%) 13	1 / 173 (0.58%) 1	1 / 82 (1.22%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2017	<p>The primary changes in this amendment are presented below:</p> <ul style="list-style-type: none">• Revised the key secondary efficacy endpoints as follows:<ul style="list-style-type: none">- Moved the endpoint on mean AUC0-72 of the NRS-A for HTX-011 vs bupivacaine HCl to be the first (#1) key secondary endpoint.- Added a key secondary endpoint (#3) on the proportion of subjects who are opioid-free through 72 hours for HTX-011 vs bupivacaine HCl.- Moved the endpoint on mean total postoperative opioid consumption through 72 hours for HTX-011 compared with bupivacaine HCl to be a key secondary efficacy endpoint (#4).- Revised the analysis plan for testing key secondary endpoints to be hierarchical testing.• Reduced the number of other (non-key) secondary efficacy endpoints.• Moved the secondary study objective on efficacy and duration of analgesia for HTX-011 vs bupivacaine HCl to be the first secondary objective.• Increased the sample size of the HTX-011 group (from 150 subjects to 200 subjects) and the bupivacaine HCl group (from 100 subjects to 200 subjects).• Increased the volume of saline placebo to be administered (from 6.8 mL to 10.3 mL).• Revised instructions on administering HTX-011 and saline placebo via instillation.• Added acetaminophen as a rescue medication.• Removed acetaminophen from the list of prohibited medications.• Revised the instructions for postoperative pain management after 72 hours and included an appendix with discharge instructions for subjects who were medically ready for discharge.• Added an exclusion criterion for systemic steroids administered within 5 half-lives or 10 days prior to administration of study drug, whichever was longer (exclusion criterion #12).• Clarified the prescribed activity for NRS-A.• Clarified how to perform NRS-R assessments.
30 July 2017	<p>The primary changes in this amendment are presented below:</p> <ul style="list-style-type: none">• Reduced the study sample size from 500 subjects to 400 subjects. The randomization scheme will remain the same.• Added Local Anesthetic Systemic Toxicity (LAST) assessments.• Added body temperature measurement and increased the number of vital sign assessment timepoints.• Specified the route of administration for acetaminophen (oral) as a rescue medication for postoperative pain.• Clarified that intraoperative safety monitoring would be in accordance with ASA standards, which is consistent with the European Board of Anaesthesiology (EBA) recommendations for minimal monitoring during Anaesthesia and Recovery.• Clarified study suspension and study stopping criteria.• Provided rationale for fentanyl dosing during surgery.• Provided additional details regarding Sponsor safety oversight.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

