Clinical trial results:
Interest of parasternal block to prevent hypertensive and tachycardia episodes during sternotomy in patients undergoing coronary artery bypass graft

Summary

EudraCT number	2018-002842-35
Trial protocol	FR
Global end of trial date	07 November 2019

Results information

Result version number	v1 (current)
This version publication date	06 November 2020
First version publication date	06 November 2020

Trial information

Trial identification

Sponsor protocol code	2018/07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03734159
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CMC Ambroise Paré
Sponsor organisation address	27 boulevard Victor Hugo, Neuilly-sur-Seine, France, 92200
Public contact	Service Recherche Clinique, CMC Ambroise Paré, +33 146415079, recherche@clinique-a-pare.fr
Scientific contact	Service Recherche Clinique, CMC Ambroise Paré, +33 146415079, recherche@clinique-a-pare.fr

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	31 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2019
Global end of trial reached?	Yes
Global end of trial date	07 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Show that the preoperative realization of a parasternal block reduces the posology of remifentanil administered during sternotomies

Protection of trial subjects:

This clinical trial was approved by a Committee for Protection of Human Subjects (CPP EST 1-2018/67 N°SI 18.08.28.61039) and the french national agency for medicines and health products safety (ANSM MEDAECNAT-2018-08-00068). The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice. Prior to inclusion, written informed consent was obtained from all subjects after a thorough oral and written participant information had been given.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2018
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	France: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	10
From 65 to 84 years	24
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were included from December 2018 to June 2019.
Patients scheduled for coronary artery bypass graft surgery were informed of the study protocol during the preanesthesia visit. They were included never later than the day before the surgery after signing informed consent.

Pre-assignment

Screening details:

Exclusion criteria : refusal to participate, age <18 years, emergency, contraindications to one or more medications of the protocol, cognitive impairment, major renal failure, chronic pain syndrome, peripheral neuropathy, coexisting hematologic disorders, hypovolemia, corticosteroid or immunosuppressive treatment

Period 1

Period 1 title	Overall period (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	Placebo

Arm description:

sodium chloride injection

Arm type	Placebo
Investigational medicinal product name	sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Infiltration

Dosage and administration details:

Injection of 60 ml of sodium chloride 0.9% divided into 4 injections of 15 ml (2 per side, between ribs 2 and 3 and between ribs 4 and 5)

Arm title	Ropivacaine

Arm description:

preoperative parasternal block by ropivacaine injection

Arm type	Experimental
Investigational medicinal product name	Ropivacaine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Infiltration

Dosage and administration details:

Injection of 60 ml of ropivacaine 0.25% divided into 4 injections of 15 ml (2 per side, between ribs 2 and 3 and between ribs 4 and 5)

Number of subjects in period 1	Placebo	Ropivacaine
Started	17	18
Completed	15	15
Not completed	2	3
Protocol deviation	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: sodium chloride injection	
Reporting group title	Ropivacaine
Reporting group description: preoperative parasternal block by ropivacaine injection	

Reporting group values	Placebo	Ropivacaine	Total
Number of subjects	17	18	35
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)	5	5	10
From 65-84 years	11	13	24
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	68.5	69.3	
standard deviation	± 10.0	± 7.8	-
Gender categorical Units: Subjects			
Female	3	4	7
Male	14	14	28
Smoking status Units: Subjects			
Never	9	6	15
Former	6	9	15
Current	2	3	5
Hypertension Units: Subjects			
Yes	15	12	27
No	2	6	8
Diabetes Units: Subjects			
Yes	7	4	11
No	10	14	24
Heart failure Units: Subjects			
Yes	2	1	3

No	15	17	32
Stroke Units: Subjects			
Yes	3	0	3
No	14	18	32
Chronic obstructive pulmonary disease Units: Subjects			
Yes	2	3	5
No	15	15	30
Cancer Units: Subjects			
Yes	3	4	7
No	14	14	28
Renal failure Units: Subjects			
Yes	1	0	1
No	16	18	34
Alcohol Units: Subjects			
Yes	1	2	3
No	16	16	32
BMI Units: kilogram(s)/square meter			
arithmetic mean	26.5	25.3	
standard deviation	± 3.3	± 3.8	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: sodium chloride injection	
Reporting group title	Ropivacaine
Reporting group description: preoperative parasternal block by ropivacaine injection	

Primary: Maximal remifentanil concentration during sternotomy

End point title	Maximal remifentanil concentration during sternotomy
End point description: Maximal dose of remifentanil (morphine peak) required to maintain hemodynamic parameters (arterial blood pressure and heart rate) in the appropriate values during skin incision, sternotomy and sternal retractor setup	
End point type	Primary
End point timeframe: during sternotomy : from skin incision to sternal retractor setup	

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: nanogram(s)/millilitre(s)				
median (inter-quartile range (Q1-Q3))	7.0 (5.2 to 8.0)	4.2 (2.5 to 6.0)		

Statistical analyses

Statistical analysis title	Max remifentanil Ce during sternotomy
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Secondary: Maximum propofol concentration during sternotomy

End point title	Maximum propofol concentration during sternotomy

End point description:

Maximal dose of propofol (hypnotic peak) required to maintain hemodynamic parameters (arterial blood pressure and heart rate) in the appropriate values during skin incision, sternotomy and sternal retractor

setup

End point type	Secondary

End point timeframe:

during sternotomy : from skin incision to sternal retractor setup

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)	4.97 (± 1.52)	3.88 (± 1.10)		

Statistical analyses

Statistical analysis title	Max propofol Ce during sternotomy
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	t-test, 2-sided

Secondary: Dose of hypnotic drug during surgery

End point title	Dose of hypnotic drug during surgery

End point description:

Total amount of propofol administered during surgery

End point type	Secondary

End point timeframe:

Intraoperative period : from induction of anesthesia to skin closure

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: milligram(s)/kilogram/hour				
arithmetic mean (standard deviation)	6.27 (± 1.46)	5.46 (± 1.21)		

Statistical analyses

Statistical analysis title	Amount of propofol
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	t-test, 2-sided

Secondary: Dose of analgesic drug during surgery

End point title	Dose of analgesic drug during surgery

End point description:

Total amount of remifentanil administered during surgery

End point type	Secondary

End point timeframe:

Intraoperative period : from induction of anesthesia to skin closure

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: microgram(s)/kilogram/hour				
arithmetic mean (standard deviation)	6.43 (± 1.86)	5.25 (± 1.41)		

Statistical analyses

Statistical analysis title	Amount of remifentanil
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	t-test, 2-sided

Secondary: Hemodynamic response : heart rate variation

End point title	Hemodynamic response : heart rate variation

End point description:

ΔHR during sternotomy, defined by the difference between the maximal HR reached during sternotomy and the baseline HR0

End point type	Secondary

End point timeframe:

Intraoperative period : from the start of general anesthesia maintenance to the fifth minute after sternal retractor setup

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: bpm				
median (inter-quartile range (Q1-Q3))	13.5 (5.7 to 21.5)	9.0 (5.5 to 15.0)		

Statistical analyses

Statistical analysis title	Heart rate variation
Comparison groups	Ropivacaine v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Wilcoxon (Mann-Whitney)

Secondary: Hemodynamic response : systolic arterial blood pressure variation

End point title	Hemodynamic response : systolic arterial blood pressure variation

End point description:

ΔSBP, defined by the difference between the maximal SBP reached during sternotomy and the baseline SBP0

End point type	Secondary

End point timeframe:

Intraoperative period : from the start of general anesthesia maintenance to the fifth minute after sternal retractor setup

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: mmHg				
arithmetic mean (standard deviation)	38.4 (± 17.8)	38.7 (± 14.7)		

Statistical analyses

Statistical analysis title	Blood pressure variation
Comparison groups	Placebo v Ropivacaine

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	t-test, 2-sided

Secondary: Hemodynamic response : average patient state index

End point title	Hemodynamic response : average patient state index

End point description:

Measure of patient state index ranging from 0 to 100 (0=very deep anesthesia, 100=no hypnotic state)

End point type	Secondary

End point timeframe:

Intraoperative period : from the start of general anesthesia maintenance to the fifth minute after sternal retractor setup

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: No unit				
arithmetic mean (standard deviation)	20.8 (± 7.7)	24.9 (± 8.0)		

Statistical analyses

Statistical analysis title	Average PSI
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	t-test, 2-sided

Secondary: Hemodynamic response : minimum patient state index

End point title	Hemodynamic response : minimum patient state index

End point description:

Measure of patient state index ranging from 0 to 100 (0=very deep anesthesia, 100=no hypnotic state)

End point type	Secondary

End point timeframe:

Intraoperative period : from the start of general anesthesia maintenance to the fifth minute after sternal retractor setup

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	18		
Units: No unit				
arithmetic mean (standard deviation)	11.7 (± 8.7)	18.3 (± 6.8)		

Statistical analyses

Statistical analysis title	Minimum PSI
Comparison groups	Ropivacaine v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	t-test, 2-sided

Secondary: Pain level during extubation

End point title	Pain level during extubation
End point description: Numeric scale of pain, ranging from 0 to 10 (0 = no pain, 10= worst possible pain)	
End point type	Secondary
End point timeframe: During extubation	

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: No unit				
median (inter-quartile range (Q1-Q3))	4 (2 to 6)	5 (2 to 6)		

Statistical analyses

Statistical analysis title	Pain score at extubation
Comparison groups	Placebo v Ropivacaine

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Wilcoxon (Mann-Whitney)

Secondary: Inflammatory response

End point title	Inflammatory response

End point description:

Serum concentrations of cytokines : MCP-1, IFN-α2, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17A, IL-18, IL-23, IL-33, TNF-α
Note : 9999 = N/A (not applicable)

End point type	Secondary

End point timeframe:

7 days

End point values	Placebo	Ropivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: picogram(s)/millilitre				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)		

Attachments (see zip file)	Inflammatory response/Inflammatory response PARA.pdf

Statistical analyses

Statistical analysis title	MCP-1
Comparison groups	Ropivacaine v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA

Statistical analysis title	IL-8
Comparison groups	Placebo v Ropivacaine

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANOVA

Statistical analysis title	IL-18
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANOVA

Statistical analysis title	IL-6
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.782
Method	ANOVA

Statistical analysis title	IL-10
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.777
Method	ANOVA

Statistical analysis title	IL-17A
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.184
Method	ANOVA

Statistical analysis title	IL-1beta
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.265
Method	ANOVA

Statistical analysis title	IL-12p70
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153
Method	ANOVA

Statistical analysis title	TNF-alpha
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.383
Method	ANOVA

Statistical analysis title	IFN-alpha2
Comparison groups	Ropivacaine v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.222
Method	ANOVA

Statistical analysis title	IL-23
Comparison groups	Ropivacaine v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANOVA

Statistical analysis title	IL-33
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	ANOVA

Statistical analysis title	IFN-gamma
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	ANOVA

Statistical analysis title	CRP
Comparison groups	Placebo v Ropivacaine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From time of inclusion to 7 days after surgery	
Adverse event reporting additional description:	
All adverse events were evaluated and followed-up by a specialist anesthetist.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ropivacaine
Reporting group description: -	

Serious adverse events	Placebo	Ropivacaine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	2 / 18 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Bradycardia	Additional description: Serious bradycardia (< 35 bpm)		
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactoid reaction	Additional description: Anaphylactoid reaction due to plasmion		
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	Ropivacaine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 17 (82.35%)	15 / 18 (83.33%)	

Vascular disorders			
Hypertension	Additional description: Hypertension requiring treatment		
subjects affected / exposed	10 / 17 (58.82%)	7 / 18 (38.89%)	
occurrences (all)	17	10	
Hypotension	Additional description: Hypotension requiring treatment		
subjects affected / exposed	7 / 17 (41.18%)	11 / 18 (61.11%)	
occurrences (all)	14	20	
Cardiac disorders			
Tachycardia	Additional description: Tachycardia requiring treatment		
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Bradycardia	Additional description: Bradycardia requiring treatment		
subjects affected / exposed	1 / 17 (5.88%)	2 / 18 (11.11%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Diaphragmatic disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Cognitive disorder			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Infections and infestations			
Pneumopathy			
subjects affected / exposed	2 / 17 (11.76%)	2 / 18 (11.11%)	
occurrences (all)	2	2	

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