Clinical trial results:
High volume PCEA versus PIEB for labor analgesia: a randomized, double-blind multicenter non-inferiority study in nulliparous women.

Summary

EudraCT number	2019-003319-76
Trial protocol	BE
Global end of trial date	10 January 2022

Results information

Result version number	v1 (current)
This version publication date	29 September 2022
First version publication date	29 September 2022

Trial information

Trial identification

Sponsor protocol code	MVDV/ER082019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 48, Leuven, Belgium,
Public contact	Research Anesthesiology, University Hospitals Leuven, christel.huygens@uzleuven.be
Scientific contact	Research Anesthesiology, University Hospitals Leuven, christel.huygens@uzleuven.be

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	10 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2021
Global end of trial reached?	Yes
Global end of trial date	10 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of our study was to compaire two techniques to maintain labour analgesia, Programmed intermittent epidural boluses (PIEB) plus patient controlled epidural analgesia (PCEA) and high volume PCEA without background infusion, on the incidence of breakthrough pain

Protection of trial subjects:

There was a constant follow-up of the patient during labour when the maintenance epidural therapy was administered and there was an immediate management of breakthrough pain by adding a supplemental bolus of epidural analgesia to the patient.

Background therapy:

Irrespective of group allocation, labour pain was initially treated with spinal administration of ropivacaine and sufentanil using a CSE (combined spinale epidural) technique. An epidural catheter was inserted and the maintenance epidural therapy was started according to group assignment.

Evidence for comparator:

PIEB has proven to be a very good maintenance therapy for labour analgesia and has been extensively compared to PCEA with background infusion. In these studies PIEB is superior to PCEA with background infusion. Bolus techniques have been proven to increase epidural spread compared to infusion techniques. A PCEA (bolus technique) without background infusion but with equal high-volume boluses has not been compared to PIEB.

Actual start date of recruitment	01 October 2019
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: 360
Worldwide total number of subjects	360
EEA total number of subjects	360

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)	360
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between februari 1 2020 and June 30 2021 we screened 399 patients in UZLeuven and GZA St Augustinus of whom 360 were randomised

Pre-assignment

Screening details:

Singleton, term pregnancies, ASA PS II, in active labour werre included.
Patients were not recruited if : ASA III or IV, known allergies to the study drug, contra-indication for neuraxial analgesia, < 18 years old, cervical dilation >7, did not understand Dutch.

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	Investigator, Monitor, Subject

Blinding implementation details:

Women were randomly allocated to the two study groups using a computer-generated block randomisation list (variable block-size with 1:1 allocation). Allocation concealment was achieved using opaque sealed envelopes containing group assignment, sequentially numbered. An anaesthetist not involved in patient management or data collection opened the envelope after oral and written informed consent and started the epidural maintenance regime according to the assigned group.

Arms

Are arms mutually exclusive?	Yes
Arm title	PCEA

Arm description:

After spinal administration of local anaesthetic analgesia, the maintenance pump was started in the PCEA (patient controlled epidural analgesia)-modus and labour analgesia was maintained using this PCEA-modus.

Arm type	Active comparator
Investigational medicinal product name	Naropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

Naropin 0.12%

Arm title	PIEB

Arm description:

After spinal administration of local anaesthetic analgesia, the maintenance pump was started in the PIEB (programmed intermittent epidural bolus)-modus and labour analgesia was maintained using this PIEB-modus.

Arm type	Experimental
Investigational medicinal product name	Naropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

Naropin 0.12%

Number of subjects in period 1	PCEA	PIEB
Started	180	180
Completed	170	166
Not completed	10	14
conversion to caesarean section	2	2
epidural catheter failure	3	7
Protocol deviation	5	5

Baseline characteristics

Reporting groups	
Reporting group title	PCEA
Reporting group description:	
After spinal administration of local anaesthetic analgesia, the maintenance pump was started in the PCEA (patient controlled epidural analgesia)-modus and labour analgesia was maintained using this PCEA-modus.	
Reporting group title	PIEB
Reporting group description:	
After spinal administration of local anaesthetic analgesia, the maintenance pump was started in the PIEB (programmed intermittent epidural bolus)-modus and labour analgesia was maintained using this PIEB-modus.	

Reporting group values	PCEA	PIEB	Total
Number of subjects	180	180	360
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)	180	180	360
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Pregnant women			
Units: Subjects			
Female	180	180	360
Male	0	0	0

End points

End points reporting groups

Reporting group title	PCEA
Reporting group description:	
After spinal administration of local anaesthetic analgesia, the maintenance pump was started in the PCEA (patient controlled epidural analgesia)-modus and labour analgesia was maintained using this PCEA-modus.	
Reporting group title	PIEB
Reporting group description:	
After spinal administration of local anaesthetic analgesia, the maintenance pump was started in the PIEB (programmed intermittent epidural bolus)-modus and labour analgesia was maintained using this PIEB-modus.	

Primary: Breakthrough pain

End point title	Breakthrough pain
End point description:	
A painscore of > 30 on a visual analogue scale	
End point type	Primary
End point timeframe:	
The occurrence of breakthrough pain during labour	

End point values	PCEA	PIEB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	166		
Units: number of patients	19	18		

Statistical analyses

Statistical analysis title	Primary outcome
Comparison groups	PCEA v PIEB
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.05
Method	Farrington-Manning
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.03
upper limit	6.36

Secondary: local anesthetic consumption	
End point title	local anesthetic consumption
End point description: The amount of local anaesthetic solution used during labour	
End point type	Secondary
End point timeframe: During labour	

End point values	PCEA	PIEB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	166		
Units: milliliters	48	60		

Statistical analyses

Statistical analysis title	Local anesthetic consumption
Comparison groups	PCEA v PIEB
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	independent t-test
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.6
upper limit	-4.7

Secondary: Satisfaction scores at 1 and 24 hours post-delivery	
End point title	Satisfaction scores at 1 and 24 hours post-delivery
End point description: A satisfaction score was asked at 1 hour (0-100) and 24 hours (0-10) after delivery of the baby	
End point type	Secondary
End point timeframe: One hour after delivery and 24 hours after delivery satisfaction scores were recorded.	

End point values	PCEA	PIEB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	166		
Units: VAS at 1 and NRS scores at 24 hours	100	100		

Statistical analyses

Statistical analysis title	Satisfaction scores at 1 and 24 hours
Comparison groups	PCEA v PIEB
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.55

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from enrollment untill the first 24 hours after delivery of the baby	
Adverse event reporting additional description: Nausea/Vomiting, neurologic deficit, adverse neonatal outcome	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25

Reporting groups	
Reporting group title	PCEA
Reporting group description: -	
Reporting group title	PIEB
Reporting group description: -	

Serious adverse events	PCEA	PIEB	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 170 (0.00%)	0 / 166 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	PCEA	PIEB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 170 (8.24%)	17 / 166 (10.24%)	
Pregnancy, puerperium and perinatal conditions			
nausea/Vomiting	Additional description: The occurrence of nausea or vomiting at least once during labour		
subjects affected / exposed	10 / 170 (5.88%)	14 / 166 (8.43%)	
occurrences (all)	10	14	
admission NICU	Additional description: The admission of the baby after delivery to the neonatal intensive care unit		
subjects affected / exposed	4 / 170 (2.35%)	3 / 166 (1.81%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2020	Change of PI and increase of inclusions after interim analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported