Clinical trial results:
Pharmacodynamics of Liposomal Bupivacaine for Peripheral Nerve Blockade: A Randomized, Triple-blinded, Cross Over Study in Volunteers

Summary

EudraCT number	2023-000035-74
Trial protocol	AT
Global end of trial date	22 October 2023

Results information

Result version number	v1 (current)
This version publication date	01 June 2024
First version publication date	01 June 2024
Summary attachment (see zip file)	Journal Article (Liposomal Bupivacaine_Anesthesiology 2024.pdf)

Trial information

Trial identification

Sponsor protocol code	1.3_19.04.2023

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Department of Clinical Pharmcology, Medical University Vienna, klin-pharmakologie@meduniwien.ac.at
Scientific contact	Department of Clinical Pharmcology, Medical University Vienna, klin-pharmakologie@meduniwien.ac.at

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	22 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2023
Global end of trial reached?	Yes
Global end of trial date	22 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective: Duration of sensory nerve blockade

Protection of trial subjects:

Trial subjects were monitored during the whole study. One week after the last visit there was a control phone call.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2023
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	Austria: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

27 subjects (healthy volunteers) have been assessed for eligibility and have been recruited.
After finishing the first study day 2 subjects of the 27 declined to participate on the second study day. These 2 subjects were excluded.

Pre-assignment

Screening details:

Healthy volunteers aged 18 to 55 yr (body mass index, 18 to 35 kg/m2) were recruited via the Department of Clinical Pharmacology (Medical University of Vienna). Explanation regarding the purpose and risks associated with the study and written informed consent was performed in accordance with the standards of the Department of Clinical

Period 1

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

Blinding implementation details:

The trail was a triple-blinded cross-over study.
Neither the physician who performed the ulnar nerve block, nor the physicians executing the sensory and motor tests nor the study participants knew which drug was administered at which study day. The sequence was determined by the randomization.

Arms

Are arms mutually exclusive?	No
Arm title	Exparel

Arm description:

Each subject received an ulnar nerve block with Exparel (liposomal bupivacaine).
Two subjects who were treated with Exparel on the first study day withdraw their consent after this first study day. These two subjects were excluded from the study.

Arm type	Experimental
Investigational medicinal product name	Exparel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Perineural use

Dosage and administration details:

The nerve block was performed with 13.3mg Exparel

Arm title	Bupivacaine

Arm description:

Each subject received an ulnar nerve block with plain bupivacaine.

Arm type	Active comparator
Investigational medicinal product name	Carbostesin
Investigational medicinal product code	
Other name	Bupivacaine
Pharmaceutical forms	Solution for injection
Routes of administration	Perineural use

Dosage and administration details:
Each subject received 15mg bupivacaine

Number of subjects in period 1	Exparel	Bupivacaine
Started	27	25
Study day 1	27	25
Study day 2	25	25
Completed	25	25
Not completed	2	0
Consent withdrawn by subject	2	-

Baseline characteristics

Reporting groups

Reporting group title	Exparel

Reporting group description:

Each subject received an ulnar nerve block with Exparel (liposomal bupivacaine).
Two subjects who were treated with Exparel on the first study day withdraw their consent after this first study day. These two subjects were excluded from the study.

Reporting group title	Bupivacaine

Reporting group description:

Each subject received an ulnar nerve block with plain bupivacaine.

Reporting group values	Exparel	Bupivacaine	Total
Number of subjects	27	25	27
Age categorical			
all study participants were healthy volunteers aged 18-55 years			
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)	27	25	27
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	13	13	13
Male	14	12	14

Subject analysis sets

Subject analysis set title	Study day 1 and 2
Subject analysis set type	Full analysis

Subject analysis set description:

As two subjects declined to participate on study day 2 they were excluded

Reporting group values	Study day 1 and 2		
Number of subjects	25		
Age categorical			
all study participants were healthy volunteers aged 18-55 years			
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)	25		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	13		
Male	12		

End points

End points reporting groups

Reporting group title	Exparel
Reporting group description:	
Each subject received an ulnar nerve block with Exparel (liposomal bupivacaine). Two subjects who were treated with Exparel on the first study day withdraw their consent after this first study day. These two subjects were excluded from the study.	
Reporting group title	Bupivacaine
Reporting group description:	
Each subject received an ulnar nerve block with plain bupivacaine.	
Subject analysis set title	Study day 1 and 2
Subject analysis set type	Full analysis
Subject analysis set description:	
As two subjects declined to participate on study day 2 they were excluded	

Primary: Success of sensory blockade

End point title	Success of sensory blockade
End point description:	
End point type	Primary
End point timeframe:	
whole study period	

End point values	Exparel	Bupivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: subjects	8	25		

Statistical analyses

Statistical analysis title	Success of sensory blockade
Statistical analysis description:	
The study was designed in a cross over manner - so each subject received two nerve blocks - once with liposomal bupivacaine and once with plain bupivacaine. In this setting each participant was their own control.	
Comparison groups	Exparel v Bupivacaine
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	Wilcoxon and McNemar

Notes:

[1] - Wilcoxon signed-rank tests were used for nonparametric paired samples and exact McNemar’s tests to compare the primary endpoint of the study, namely the success of sensory blockade.

[2] - two-tailed

Primary: Duration of sensory blockade

End point title	Duration of sensory blockade

End point description:

End point type	Primary

End point timeframe:

Duration of sensory blockade was measured after ulnar nerve block. The study was designed in a cross over manner - each subject received two nerve blocks - once with Exparel and once with bupivacaine.

End point values	Exparel	Bupivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: minute				
median (inter-quartile range (Q1-Q3))	375 (345 to 435)	562 (450 to 610)		

Statistical analyses

Statistical analysis title	Duration of sensory blockade
Comparison groups	Exparel v Bupivacaine
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05 [4]
Method	Wilcoxon and McNemar

Notes:

[3] - Wilcoxon signed-rank tests were used for nonparametric paired samples and exact McNemar’s tests to compare the primary endpoint of the study.
[4] - two-tailed

Secondary: Onset of sensory blockade

End point title	Onset of sensory blockade

End point description:

End point type	Secondary

End point timeframe:

measured after each nerve blockade

End point values	Exparel	Bupivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: minute				
median (inter-quartile range (Q1-Q3))	105 (60 to 150)	15 (10 to 30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Success of motor blockade

End point title	Success of motor blockade

End point description:

End point type	Secondary

End point timeframe:

measured after each nerve block

End point values	Exparel	Bupivacaine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: subject	0	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Exparel
Reporting group description:	
One study participant reported experiencing muscle pain at the injection site after the administration of Exparel. The pain spontaneously resolved within 24 h after administration of Exparel.	
Reporting group title	Bupivacaine
Reporting group description:	
no adverse events in this reporting group	

Serious adverse events	Exparel	Bupivacaine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (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: 3 %

Non-serious adverse events	Exparel	Bupivacaine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
Skin and subcutaneous tissue disorders			
Muscle discomfort	Additional description: One volunteer (no. 17) reported experiencing muscle pain in the puncture area, which spontaneously resolved within 24 h after administration of liposomal bupivacaine.		
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	
occurrences (all)	1	0	

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

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

Obviously, our study was conducted in volunteers without undergoing surgery. These trials have their drawbacks. Thus, studies comparing sensory testing methods in volunteers with the clinical setting of postoperative analgesia are needed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38558118