# 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<br>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<br>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).<br>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