1. COVER PAGE

1. Official title:

Informed consent form of the study (ID: NCT04385966) entitled “Diaphragmatic paralysis after interscalene brachial plexus block: a randomized, double-blinded, unicenter and controlled clinical trial to reduce the dose of levobupivacaine 0,25% 20 ml to 10 ml undergoing arthroscopic shoulder surgery”.

2. NCT number:

NCT04385966

3. Document date:

December 19th, 2019

PATIENT INFORMATION SHEET

Study title	**SINGLE-CENTER RANDOMIZED DOUBLE-BLIND PHASE III CLINICAL TRIAL AIMED AT DEMONSTRATING A LOWER INCIDENCE OF ACUTE DIAPHRAGMATIC PARALYSIS FOLLOWING INTERSCALENE BRACHIAL PLEXUS BLOCK IN SHOULDER ARTHROSCOPIC SURGERY WITH ADMINISTRATION OF 25 MG VS. 50 MG OF 0.25% LEVOBUPIVACAINE**
Protocol code	**REDOLEV-2019.**
Promoter	**Instituto de Investigación Sanitaria Aragón**
Principal investigator	**Pablo Oliver Forniés MD** **Email:** poliverf@salud.aragon.es **Phone:** +34 685 962 086
Center	**Department of Anesthesiology, Reanimation and Pain Management. University Hospital Miguel Servet. Zaragoza. Spain.**

1. INTRODUCTION:

It is our pleasure to **invite you to participate in a clinical trial we are about to begin.** The trial has been approved by the Drug Research Ethics Committee of the hospital and by the Spanish Agency for Medicines and Health Products (AEMPS), in accordance with Spanish Royal Decree 1090/2015 of 4 December and European Regulation 536/2014/EEC of 16 April, which regulate the performance of drug-based clinical trials.

Our goal is to provide you with enough detailed information to allow you to **decide whether you would agree (or decline) to participate in the study**. You are requested to read this information sheet carefully and get back to us in case you have any doubts or queries.

Needless to say, you may consult with as many people as you deem appropriate prior to making your final decision.

2. YOUR PARTICIPATION IS VOLUNTARY

We are inviting you to participate in this study because **you are due to be undergo elective shoulder arthroscopic surgery at the Orthopedic and Trauma Surgery Department.** Prior to the procedure, the Anesthesia and Resuscitation Department of the University Hospital Miguel Servet will anesthetize the operative area by injection of an anesthetic agent into your neck. Specifically, local anesthetics will be administered around a group of nerves located between your neck and your armpit called the brachial plexus. This is known as an interscalene brachial plexus block (IBPB). To perform this nerve block, the area to be anesthetized must be identified by ultrasounds, a painless, non-invasive and radiation-free technique that uses sound waves to produce images.

Please be advised that your participation in this study would be **voluntary** and you may decide **NOT** to participate. Should you decide to participate, you may change your mind and withdraw your consent at any time, without this affecting your relationship with your doctor and without any prejudice to your treatment.

Agreeing to participate in this study means giving your consent to being examined by ultrasounds and spirometry and granting us access to your hospital medical records.

3. PURPOSE OF THE STUDY

The research is motivated by the high incidence of respiratory complications observed following administration of locoregional anesthesia to the shoulder during shoulder arthroscopic surgery. Our hypothesis is that a reduction of the dose of the anesthetic agent customarily used for brachial plexus blocks might mitigate these side effects.

The main goal of the study is to **demonstrate a decreased incidence of acute diaphragmatic paralysis diagnosed by ultrasound following IBPB in shoulder arthroscopic surgery with administration of 10 ml of 0.25% levobupivacaine (25 mg dose) as compared with 20 ml of 0.25% levobupivacaine (50 mg dose)**.

4. STUDY DESCRIPTION

The study will consist in observing the clinical impact on the diaphragm (a muscle located beneath our lungs that control sour breathing) of the administration of a local anesthetic agent by ultrasounds and spirometry. A IBPB will be performed and the local anesthetic will be placed around the nerves responsible for shoulder sensitivity in the course of our current practice. Spirometry is a respiratory test where the patient is asked to blow as fast and as hard as they can through a mouthpiece to check the status of their respiratory function.

The drug administered will be **chirocane® 2.5 mg/ml (0.25% levobupivacaíne)** solution for injection or infusion. You will be assigned to one of two possible patient groups: subjects in **group 1** will be administered

20 ml of chirocane® 2.5 mg/ml (50 mg dose), while those in **group 2** will receive **10 ml (25 mg dose).** Both the drug itself and the doses to be administered to the two groups are the same ones we use in daily practice, which means that you would be receiving them anyway even if you decided not to participate in the study.

Assignment to the study groups (group 1 or group 2) will be done **randomly**, with a 50% chance of being assigned to either group.

A total of **48 patients** of your same characteristics will be recruited for the study.

The study does not require subjects to fill out any questionnaires. Nor do they have to make any additional hospital visits or provide any biological samples.

5. ACTIVITIES UNDER THE STUDY

During the study, each patient will be **followed up** for approximately **24 hours**. The treatment phase, i.e. when the patient is under the effect of the local anesthetic, will last between 6 and 8 hours, which is the duration of action of the drug. It is expected that collecting the data from all 48 patients will take 4 months altogether.

These two interventions will be performed in the course of **four visits**: two pre-op (in a hospital ward and in the pre-surgery room) and two post-op, one in the post-anesthesia care unit (PACU) at one hour post-op and the other in the ward at 24 hours post-op.

PARTICIPATION CALENDAR			
ADMISSION	**PRE-OP**	**1 HOUR POST-OP**	**24 HOURS POST-OP**
- INTERVIEW - DELIVERY OF INFORMATION SHEET - SIGNING OF INFORMED CONSENT FORM	- ULTRASOUND - SPIROMETRY.	- INTERVIEW - ULTRASOUND - SPIROMETRY	- INTERVIEW - SPIROMETRY END OF PARTICIPATION
HOSPITAL WARD	*PRE-SURGERY ROOM*	*PACU*	*HOSPITAL WARD*

Two interventions will be performed as part of the study: a bilateral **thoracic ultrasounds** of the diaphragm and a **spirometry performed with a handheld device**. Ultrasonography is a painless non-invasive and radiation-free diagnostic test that uses ultrasound waves to view the internal structures of the body. A spirometry is a breathing test where the patient successively and repeatedly inspires fully and then expires all the air out of the lungs through a respiratory flow measuring device equipped with a disposable mouthpiece.

6. RISKS AND INCONVENIENCIES DERIVED FROM YOUR PARTICIPATION IN THE STUDY

The drug under investigation, **chirocane® 2.5 mg/ml solution for injection or infusion, is administered as per its approved indication, its commercial distribution being approved by the Spanish Agency for Medicines and Health Products (nr 63171)**. AbbVie Spain, S.L.U. is the marketing authorization holder for the product. The authorization was first granted on 18 December 1998 and renewed on 10 March 2015.

Potential side effects of the drug include hypotension, nausea, anemia, vomiting, dizziness, headache, fever, pain during the procedure, allergy, etc. As the drug was approved by the corresponding health authorities, information on its side effects is publicly available. Please contact the principal investigator for a full list of the side effects associated with this drug. In any event, you will be provided with the drug label.

The two diagnostic techniques to be used in this study (ultrasonography and spirometry) are **painless, non-invasive, radiation-free and are carried out as part of ordinary clinical practice.** This means that you would have to undergo them even if you chose not to participate in the study.

The research project does not involve the performance of any additional invasive procedure other than those carried out as standard anesthetic practice by the hospital's Anesthesia and Resuscitation Unit for elective surgical procedures.

By deciding to participate in the study, you undertake to receive the prescribed medical visits and perform all the activities required.

6. POTENTIAL BENEFITS

As the study will be geared toward the generation of knowledge, it is not likely that your participation will result in any benefit for your health. However, by participating you will be contributing to furthering scientific knowledge and promoting social wellbeing.

You will not receive any economic compensation for enrolling in the study. You will nevertheless incur no economic expense as a result of your participation.

WARNING: THE COST-FREE NATURE OF THE PRODUCTS UNDER THE STUDY, AS WELL AS OF THE DIAGNOSTIC TESTS PERFORMED, THE CLOSE CLINICAL MONITORING, ETC ARE NOT TO BE CONSIDERED A BENEFIT DERIVED FROM PARTICIPATION IN THE STUDY.

7. PREGNANCY WARNING

No clinical data have been published on any teratogenic or otherwise deleterious effects of the drug under investigation on women of childbearing age or men whose female partners are of childbearing age during the first trimester of pregnancy or during breastfeeding. This means that maternal breastfeeding is permissible following its administration.

8. ALTERNATIVE TREATMENTS

The drug under investigation is the medication of choice for the type of anesthesia you are going to receive. For that reason**, it may also be administered to you even if you decided not to participate in the trial**.

The Principal Investigator can provide you with information on alternative treatments at your request.

9. INSURANCE

In accordance with the applicable legislation (Royal Decree 1090/2015) the Promoter of the study has taken out an insurance policy that provides for compensation to be awarded to subjects in case of harm and/or injury caused as a result of their participation in the study, provided that such harm and/or injuries do not arise from the condition for which surgery is needed or from the progression of the disease due to inefficacy of treatment.

The insurance policy number is 2034180 (Berkley Spain).

For further information about insurance, please contact the Principal Investigator.

10. PERSONAL DATA PROTECTION

Data protection Regulation (EU) 2016/679 of the European Parliament and of the Council (GDPR) of 27 April 2016 has been in force since 25 May 2018. For that reason, you must be aware of the following:

- In addition to the rights you are already familiar with (access to, rectification of, objection to and cancellation of data) you can now limit the processing of erroneous data, request a copy of any of your personal data being processed or ask for your data to be transferred to a third party (portability). To exercise your rights under the GDPR, please contact the Principal Investigator or the Data Protection Officer of the hospital at www.iisaragon.es .Please note that, even if you decide to drop out of the study, your data cannot be erased as this would impact the validity of the findings and prevent us from complying with our legal requirements and the medication

authorization procedures. Should you have any objections, you can contact the Data Protection Agency.

- Both the Hospital and the Promoter of the study are responsible for the processing of your data and undertake to abide by the applicable data protection regulations. The data collected for the purposes of the study will be coded so that it cannot be traced back to any individual patient. Only your doctor and/or the researchers participating in the study will be able to connect your data with your clinical record. This means that your identity will not be disclosed to anybody, except to the health authorities if requested or in case of a medical emergency. Research ethics committees, health inspectors and the Promoter (personally or through persons authorized by them) will only be allowed access to the data repository to check personal data, review the procedures under the clinical trial, and ensure compliance with clinical best practices. They are strictly required to preserve the confidentiality of the information.
- The principal Investigator and the Promoter are obliged to preserve the data collected for the trial for at least 25 years following its completion. After that, your personal data will only be maintained at the hospital for use in connection with your healthcare. Should the law and the applicable ethical requirements allow it, the Promoter may keep your data for use in other investigational projects with your explicit authorization.
- Should any of your coded data be transferred to entities in our group, to service providers or to scientists that may collaborate with us from outside the EU, such data will be protected by the data protection authorities by means of safeguards such as contracts or other mechanisms. For more information, please contact the Promoter's Data Protection Officer at www.iisaragon.es

11. EXPENSES AND ECONOMIC COMPENSATION

The Promoter of the study will be responsible for managing the funding thereof. Before commencing the trial, the Promoter must sign a contact with the Principal Investigator and the center where it will be performed. **You will not have to pay for the drugs or the diagnostic tests under the study**. Your participation will not result in any costs on top of those associated with your ordinary clinical care, if any. You will be reimbursed for any extraordinary expenses you incur in connection with the study (eg. meals and travel).

12. ADDITIONAL INFORMATION

As required by the Spanish legislation, a description of the clinical trial will be available at http://reec.aemps.es.

You will be informed as soon as possible about any new data about the drug under investigation that may be found out in the course of the trial and may affect your willingness to participate in it.

Please note that you may be excluded from the study if the Promoter or the investigators consider it appropriate for safety reasons, for any adverse event occurring during the trial or because, in their opinion,

you are not abiding by the established procedures. In any of those cases, you will be provided with a suitable explanation of your exclusion.

By signing the attached consent form you undertake to comply with the study procedures outlined in this document.

13. WHAT TREATMENT WILL I RECEIVE WHEN THE CLINICAL TRIAL IS OVER?

You will be administered the drug under investigation with the sole purpose of being anesthetized during your surgical procedure.

You are entitled to be informed about both the overall results of this study and those related to you personally. You are also entitled not to be informed about such results, if you wish so. The informed consent form contains a specific question asking you which option you prefer. Should you wish to be informed about the results, the Principal Investigator will make them available to you.

On some occasions, unexpected findings arise in the course of a clinical trial that may be relevant to the subjects' health. Should this happen in this case, we shall contact you to ask you to visit your doctor.

14. DOUBTS & QUERIES:

Should you have doubts in the course of the trial, or should you require additional information, please contact Pablo Oliver Forniés, MD at the Department of Anesthesiology, Resuscitation and Pain Management of Miguel Servet University Hospital, Paseo Isabel la Católica, 1-3, 50009 Zaragoza. Spain. Telephone number: +34 976 76 55 00. Mobile phone: +34 685 962 086. E-mail: poliverf@salud.aragon.es.

15. PROCESSING OF BIOLOGICAL SAMPLES

This study does not require the collection of any biological samples from the patients.

Thank you for your collaboration. Should you wish to participate, please sign the attached informed consent form.

. *Signed:*

Pablo Oliver Forniés MD
Anesthesiology and Resuscitation.
Miguel Servet University Hospital

INFORMED CONSENT FORM

Study title	**SINGLE-CENTER RANDOMIZED DOUBLE-BLIND PHASE III CLINICAL TRIAL AIMED AT DEMONSTRATING A LOWER INCIDENCE OF ACUTE DIAPHRAGMATIC PARALYSIS FOLLOWING INTERSCALENE BRACHIAL PLEXUS BLOCK IN SHOULDER ARTHROSCOPIC SURGERY WITH ADMINISTRATION OF 25 MG VS. 50 MG OF 0.25% LEVOBUPIVACAINE**
Protocol code	**REDOLEV-2019.**

I, ... *(subject's name and surname)*

☐ Have read the patient information sheet that was delivered to me

☐ Have been given the opportunity to ask questions about the study.

☐ Have received enough information about the study.

☐ Have spoken to Pablo Oliver Forniés, MD *(Name of the principal investigator)*

☐ Understand that my participation is voluntary.

☐ Understand that I can withdraw from the study:

1) Whenever I wish to do so

2) Without giving any explanations

3) Without this affecting the care I receive

I will receive a signed and dated copy of this informed consent form

I freely give my consent to participate in the study.

……. ……..

Subject's signature Investigator's signature

Date: ____/____/_____ Date: ____/____/_____

(Name, signature and date in the subject's own handwriting)

(To be filled out when informed consent is obtained from **differently abled persons)**

…… ……..

Signature of legal guardian, family representative or civil partner

Date: ____/____/_____

Investigator's signature

Date: ____/____/_____

I wish to be informed about any data arising from the investigation that may be relevant to my health:

☐ YES

☐ NO

…… ……

Subject's signature

Date: ____/____/_____

Investigator's signature

Date: ____/____/_____

WITNESSED INFORMED CONSENT FORM

Study title	**SINGLE-CENTER RANDOMIZED DOUBLE-BLIND PHASE III CLINICAL TRIAL AIMED AT DEMONSTRATING A LOWER INCIDENCE OF ACUTE DIAPHRAGMATIC PARALYSIS FOLLOWING INTERSCALENE BRACHIAL PLEXUS BLOCK IN SHOULDER ARTHROSCOPIC SURGERY WITH ADMINISTRATION OF 25 MG VS. 50 MG OF 0.25% LEVOBUPIVACAINE**
Protocol code	**REDOLEV-2019.**

I, ... *(witness' name and surname), acting as a witness,* declare that Mr/Mrs …….....(name and surname of the subject) has in my presence been given and read the patient information sheet concerning the present study in such a way that:

☐ He/she has been able to ask questions about the study.

☐ He/she has received enough information about the study.

☐ He/she has spoken to Pablo Oliver Forniés, MD (*name of principal investigator)*

☐ He/she understands that his/her participation is voluntary

☐ He/she understands that he/she may withdraw from the study

1) Whenever he/she wishes to do so

2) Without giving explanations

3) Without this affecting the care he/she receives

I will receive a signed and dated copy of this informed consent form.

……. ……..

Subject's signature
Date: ____/____/_____

Investigator's signature
Date: ____/____/_____

(Name, signature and date in the witness' own handwriting)

The patient wishes to be informed about any data arising from the investigation that may be relevant to their health:

☐ YES

☐ NO

…… ……

Witness' signature Investigator's signature

Date: ____/____/_____ Date: ____/____/_____

☐ The subject cannot read or write.

☐ A member of the study staff has read the document to and reviewed it with the subject, giving the latter the chance to ask questions or consult with other people.

☐ The witness must be an impartial person, unrelated to the study.