Protocol title:	**RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS.**
Protocol Code EudraCT	**QUEPRO** 2016-004117-27
Principal Investigator:	Dr. Elisa Sánchez Barrado (Anesthesiology, resuscitation and pain treatment service).
Promoter:	Institute of Biomedical Research of Salamanca (IBSAL) Complejo Asistencial Universitario de Salamanca Hospital Virgen de la Vega, 10th Floor.Paseo de San Vicente, 58-182. 37007 SalamancaTel.: +34 923 09 04 70
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PATIENT INFORMATION SHEET

INTRODUCCION

We are writing to inform you about a research study in which you are invited to participate. The study has been approved by the Ethical Committee for Research with medicines of the University Assistance Complex of Salamanca and the Spanish Agency for Medicines and Health Products, in accordance with current legislation, Royal Decree 1090/2015, of December 4, which regulates clinical trials with medicines, the Ethics Committees for Research with medicines and the Spanish Registry of Clinical Studies.

Our intention is only that you receive the correct and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. To do this, read this fact sheet carefully and we will clarify any doubts that may arise after the explanation. In addition, you can consult with the people you consider appropriate.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw consent at any time, without altering your relationship with your doctor or causing any harm to your treatment.

STUDY OVERVIEW

The study we would like you to participate in is on the prevention of delirium that occurs frequently in the period after the surgery you are going to undergo. The picture of delirium consists of an alteration in attention and consciousness, in orientation and memory, in language

and perception. Itdevelops over a short period of time (hours or days), tends to fluctuate throughout the day and representsa change from how it was before.

According to the current literature, this condition is often triggered in the hours after theintervention and is more frequent in the elderly, if they have any visual or hearing impairment or neuropsychiatric disease, such as depression, if they have atherosclerosis, diabetes mellitus, renal failure ... The fact that you develop this condition is associated with an increase in hospital stay, worsening of postoperative variablessuch as cognitive or functional status and slowing recovery after the intervention.

For this reason it is increasingly important to investigate with drugs to try to prevent this condition from developing. At present, the use of several drugs has been studied without the results having been conclusive. The drug we want to use in **QUETIAPINE**. It is a drug that belongs to the group of drugs called second-generation antipsychotics (with fewer side effects than typical antipsychotics). It is currently given to those with psychiatric disorders such as major depressive episodes, bipolar disorder, schizophrenia, moderate to severe mania. .. This drug has already been used to treat patients who develop delirium with good results and low risk to the patient.

The reason for our study is to use quetiapine with lower doses than those used so far and for a short period of time (3 days) to avoid the appearance of delirium after surgery in those patients who , like you, are at risk of developing it.

For the study to be effective and our results reliable we need a sample of 350 patients divided into two groups. One of them will receive the medication under study in the form of capsules with 25mg of quetiapine. The other group will receive a capsule identical to the previous one but which will not contain any pharmacologically active substance. Neither the doctor who dispenses it nor the patient will know what treatment he will receive. You may be randomly assigned with a 50% chance to either group The medication will be administered twice a day. It will begin 60 minutes after the intervention, in the anesthetic recovery or resuscitation unit and will be administered every 12 hours during the first 3 days of the period after surgery. A daily medical visit will be made by one of the investigators included in the trial during the first seven days after the intervention or until the moment of discharge. During this period, an electrocardiogram and a complete analysis will be performed in an extraordinary way, apart from the visits and complementary tests that will be applied within a usual postoperative period.

By agreeing to participate in this study, you are responsible for the accuracyof the information administered and for reporting any adverse events or changes in medication.

BENEFITS AND RISKS FROM YOUR PARTICIPATION IN THE STUDY

The appearance of delirium during the period after the intervention is one of the most frequent complications and is associated with more expensive and slow recovery after surgery, leaving in some cases functional and cognitive sequelae. What we hope to demonstrate with this work is that using quetiapine in small doses is able to decrease the risk of developing delirium, although you may not get any health benefit from participating in this study.

Quetiapine is a drug already marketed, with extensive experience of use and clearly defined side effects. Among the adverse effects associated with the use of quetiapine is frequent drowsiness(with a probability greater than 10%), among the usual effects (between 1-10%): asthenia, orthostatic hypotension(drop in blood pressure when changing position), increased heart rate, dry mouth, dyspepsia, constipation, weight gain, elevation of liver enzymes, dizziness, rhinitis. Uncommon adverse symptoms (0.1-1%): syncope, seizures. Every rare adverse effects (0.01-0.1%): neuroleptic malignant syndrome, grand mal crisis and jaundice. In the published literature on quetiapine the incidence of individual adverse events wasgenerally low and did not exceed 4% in either treatment group. In relation to the appearance of extrapyramidal symptoms (alteration in the quality of movements, muscle tone with stiffness and appearance of tremors) and prolongation of the QTc interval: these are two possible adverse effects associated with the type of drug that is quetiapine (antipsychotic). Quetiapine was associated with an increased incidence of extrapyramidal symptoms compared to placebo in patients treated for major depressive episodes in bipolar disorder. In clinical trials and when used according to the information included in the SmPC, quetiapine was not associated with a persistent increase in absolute QT intervals.

It should be noted that the doses proposed for this study are much lower than those used in patient groups where the use of quetiapine is indicated. With respect to the use of quetiapine in patients with a diagnosed delirium, it resolved the symptoms of delirium faster than placebo and with the same efficacy as other antipsychotics (haloperidol and misulpride), evidencing a low incidence of side effects. A higher degree of sedation was detected compared to other antipsychotics but a lower incidence of QTc prolongation and extrapyramidal symptoms. In relation to quetiapine prophylaxis for postoperative delirium there is no literature published at the present time.

ALTERNATIVE TREATMENTS

At present there is no treatment available for postoperative delirium prophylaxisthat has demonstrated efficacy.

SURE

It is a trial classified as Low level of intervention and as such, is covered by the policy subscribed by the Public Health Service of Castilla y León, SACYL, for this purpose, which complies with current legislation and will provide compensation and compensation in case of impairment of your health or injuries that may occur in relation to your participation in the study.

DATA PROTECTION AND CONFIDENTIALITY

All information about your results will be treated as strictly confidential. Your data will be identified by a code, so that it does not include information that can identify you, and only the research team can relate this data to you. The research team assumes responsibility for the

protection of personal data. Both your samples and your data will be kept under the appropriate security conditions and it is guaranteed that the subjects cannot be identified through means considered reasonable by persons other than those authorized. If the results of the study are susceptible of publication in scientific journals, in 6 no time personal data of the participants in this research will be provided. Your personal data will be protected in accordance with the provisions of Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 on Data Protection (RGPD), having the right to access, rectify or cancel your data, , and you can restrict the processing of data that is incorrect, request a copy or that the data that you have provided for the study be transferred to a third party. To exercise your rights, please contact the principal investigator of the study whose details are specified at the end of this document. You also have the right to contact the Data Protection Agency if you are not satisfied.

FINANCIAL COMPENSATION

The sponsor of the study is responsible for managing the financing of the study. To carry out the study, IBSAL, as promoter of the study, has signed a contract with the center where it is going to be carried out and with the study doctor.

Your participation in the study will not cost you any expense. You will not have to pay for study drugs.

OTHER RELEVANT INFORMATION

Any new information regarding the drugs used in the study that may affect your availability to participate in the study, which is discovered during your participation, will be communicated to you by your doctor as soon as possible.

If you decide to withdraw consent to participate in this study, no new data will be added to the database and you may require the destruction of all previously retained identifiable samples to prevent further analysis.

You should also know that you may be excluded from the study if the sponsor and study investigators deem it appropriate, either for safety reasons, for any adverse events that occur from the study medication or because they consider that you are not complying with the established procedures. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

By signing the attached consent form, you agree to comply with the study procedures that have been presented to you. When your participation ends, you will receive the best treatment available and that your doctor considers the most appropriate for your condition, but you may not be able to continue administering the study medication.

Therefore, neither the investigator nor the sponsor makes any commitment to keep such treatment out of this study.

QUESTIONS ABOUT THE STUDY

If you have further questions about the treatment and/or study, contact your doctor at the following numbers:

Number:.....

Telephone:.....
..

Thank you for reading this fact sheet.

If you agree to participate in this study, you will receive a copy of this sheet and a signed copy of the informed consent.

WRITTEN INFORMED CONSENT **BY THE PATIENT**

Protocol title:	**RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS.**
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I, (name and surname)..... ....

- I have read the information sheet given to me.
- I have been able to ask questions about the study.
- I have received enough information about the study.
- I understand that my participation is voluntary and that I can withdraw from the study:
  - 1º Whenever you want
  - 2º Without having to give explanations.
  - 3º Without this affecting my medical care.
- I freely agree to participate in the study and give my consent to the access and use of my data under the conditions detailed in the information sheet.

I have spoken to: (name of researcher) .....

Patient Signature **Investigator's signature**

Number: Number:

Date: Date:

ORAL INFORMED CONSENT **OF THE PATIENT INTHE PRESENCE OF A WITNESS**

Protocol title:	**RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS.**
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I, (name and surname of the witness)..... ..... , I declare, under my responsibility, that: (name and surname of the patient participating in the medical study)..... .....

- You have read the information sheet that has been given to me.
- You have been able to ask questions about the study.
- You have received enough information about the study.
- You understand that your participation is voluntary.
- Understand that I can withdraw from the studio:
  - 1º Whenever you want
  - 2º Without having to give explanations.
  - 3º Without this affecting my medical care.
- You have freely expressed your agreement to participate in the study and give your consent for the access and use of my data under the conditions detailed in the information sheet.

I have spoken to: (name of researcher) .....

Signature of the witness Signature of the investigator

Number: Number:
Date: Date:

WRITTEN INFORMED CONSENT OF THE LEGAL REPRESENTATIVE

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I, (name and surname) .... , as (relationship with participant) .... I declare that: (Name and surname of the patient participating in the medical study)..... .....

- You have read the information sheet that has been given to me.
- You have been able to ask questions about the study.
- You have received enough information about the study.
- You understand that your participation is voluntary.
- Understand that I can withdraw from the studio:
  - 1º Whenever you want
  - 2º Without having to give explanations.
  - 3º Without this affecting my medical care.
- You have freely expressed your agreement to participate in the study and give your consent for the access and use of my data under the conditions detailed in the information sheet.

I have spoken to: (name of researcher) .....

Signature of the representative **Signature of the researcher**

Number: Number:
Date: Date:

REVOCATION OF CONSENT

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I, D/Mrs. . I REVOKE the consent given on date ..... and I do not wish to continue participating in the present study, the treatment of which I conclude at the date of signature.

Patient Signature **Investigator's signature**

Number: Number:

Date: Date:

REVOCATION OF CONSENT IN THE PRESENCE OF A WITNESS

Protocol title:	**RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS.**
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I, (name and surname of the witness)..... HAS REVOKED its authorization to participate in this study.

Signature of the witness. **Signature of the researcher.**

Number: Number:
Date: Date:

REVOCATION OF CONSENT BY LEGAL REPRESENTATIVE

Protocol title:	**RANDOMIZED, DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL FOR QUETIAPINE PROPHYLAXIS OF POSTOPERATIVE DELIRIUM IN AT-RISK SURGICAL PATIENTS.**
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I, (name and surname) ..... I declare that: (Name and surname of the patient participating in the medical study)..... HAS REVOKED its authorization to participate in this study.

Signature of the representative **Signature of the researcher**

Number: Number:
Date: Date: