INFORMATION AND INFORMED CONSENT SHEET

Title:	**Randomised clinical trial to evaluate the dose and time of administration of indocyanine green in near-infrared fluorescein cholangiography during laparoscopic cholecystectomy:**
Code:	**DOTIG study.**
No. EudraTC	**2022-000904-36**
Version:	**2.0**
Promoter:	**Biomedical Research Institute of Salamanca (IBSAL)**
Principal Investigator	**Jaime López Sánchez MD, PhD.** **Department of General and Digestive System Surgery. Complejo Asistencial Universitario de Salamanca. Salamanca, Spain.** **Institute of Biomedical Research of Salamanca (IBSAL). University of Salamanca. Salamanca, Spain.**

Introduction

We are writing to inform you about a research study which you are invited to participate. Our intention is that you receive sufficient and correct information so that you can decide whether or not to take part in this study. To do this, please take the time to read this information sheet carefully and thoroughly and discuss it with whomever you feel appropriate. Ask the doctor or study staff to explain any words or information that you do not understand clearly, as well as any questions you may have.

If you decide to participate, we will ask you to sign the attached informed consent document. We will provide you with an original copy of this signed and dated document for you to keep and the original document will be kept on file with the rest of the study documentation.

The study has been approved by the Ethics Committee for Research with Medicines of the University Hospital of Salamanca, in accordance with current legislation, the Royal Decree 1090/2015 regulating clinical trials with medicines, the Ethics Committees for Research with Medicines and the Spanish Register of Clinical Studies, Royal Decree 1591/2009 regulating medical devices, Royal Decree 1616/2009 on active implantable medical devices (if applicable), and Circular 7/2004 of the Spanish Agency for Medicines and Medical Devices on clinical research with medical devices.

It has also been designed and will be carried out in accordance the recommendations set out in the Declaration of Helsinki and the Standards of Good Clinical Practice.

You should be aware that your participation in this study is voluntary and that you may choose NOT to participate. If you decide to participate, you may change your decision and withdraw your consent at any time without changing your relationship with your doctor or your health care.

You should also be aware that you may be withdrawn from the study if the sponsor or investigators deem it appropriate, either for safety or other reasons. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

Aim of the study

You are invited to participate in the study because you have been diagnosed with symptomatic cholelithiasis (a very common disease of the gallbladder). The standard and universally accepted treatment for your disease is removal of the gallbladder (cholecystectomy), ideally by a minimally invasive route (laparoscopy).

To avoid some of the complications that arise from laparoscopic cholecystectomy, a tool called fluorescent cholangiography has recently been developed. This technique attempts to fluorescently map critical anatomical structures that appear during surgery, using a substance called indocyanine green. This drug is usually administered intravenously and is eliminated in its entirety by bile. Thanks to the fluorescent characteristics of indocyanine green, and its biliary elimination, we will be able to obtain real-time and accurate images of the biliary anatomy. This will aid intraoperative anatomical identification and may prevent injury to important structures. However, administration interval and the exact dose of indocyanine green to obtain an accurate technique is currently not defined. The DOTIG study (Dose and administration time of indocyanine green in near-infrared fluorescein cholangiography during laparoscopic cholecystectomy) will attempt to find the optimal dose and ideal administration time for performing laparoscopic cholecystectomy with fluorescein cholangiography.

Study procedures and potential risks and discomforts

The study will be carried out in all patients who present an indication for laparoscopic gallbladder removal, accept inclusion in the study and meet the study inclusion . You will not be able to participate in this study if you have any of the following contraindications: being a minor, pregnancy or breastfeeding at the time of surgery, advanced chronic kidney disease, allergies or adverse reactions to the product, its excipients, iodinated contrasts or diseases of the thyroid gland.

The total number of patients planned to be included in the study is 160 subjects. The product to be administered is called Veryde (Diagnostic Green GMBH, Aschheim-Dornach, Germany) and contains indocyanine green sodium as active substance. All patients who agree to enter the study will be administered the drug at a variable dose and interval prior to surgery. The study will have four treatment groups divided into different doses and times. The doses will be calculated as a fixed dose or as a ratio to total body weight. The administration interval will vary from the time of admission to the hospital ward to the time of anaesthetic induction. The allocation of dose and time of administration prior to surgery shall be randomised using a computer application.

This work does not collect biological samples for research purposes and does not perform procedures or tests that are not part of routine clinical practice.

All the information on this study will be stored in coded form and will be used exclusively for the purposes specified herein. In the event that your data is transferred to other research groups, this will always be done in accordance with current legislation, keeping your data coded, in order to carry out studies related to the objectives of this work, and with the prior authorisation of the Research Ethics Committee. In the event that the objectives of the research work proposed by other research groups are different from those of the present project, you will be asked for a new consent.

Indocyanine green (Veryde) is a product authorised by the Spanish Food Safety Agency.

Medicines and Health Products (AEMPS) and the European Medicines Agency (EMA). It has been marketed since 2017 for hospital use only and in authorised diagnostic centres. Indocyanine green is approved for diagnostic use in the field of heart, brain, eyeball and liver studies. The drug has been widely used for fluorescein cholangiography since the first study was published in 2009 to the present day. It has been shown to be safe in humans, with a very low rate of adverse events.

As a drug approved by the competent health authorities, information on the side effects of indocyanine green (Veryde) is available to everyone. There may be side effects or reactions that you should be aware of. Serious allergic reactions (anaphylactic reactions) are extremely rare (affecting less than 1 in 10,000 patients). Patients with kidney disease may be more at risk of developing allergic reactions. Only two cases of death have been reported with the use indocyanine green during cardiology studies (frequency less than 1/330,000 estimated cases). Cases of indocyanine green overdose are unknown at present. No additional risks are foreseen as you will not be undergoing any procedures outside standard clinical practice.

As a participant in the study, you will be expected to fulfil a number of responsibilities as outlined below:

- Compliance with the scheduled visit during the first postoperative month.

- Report any adverse events that happen to you or changes in medication, advising that, except in an emergency, do not change the medication you are taking or take other medications or "herbal products" without first consulting with the study doctor.

Please speak to your study doctor for a full list of side effects reported with this drug and in any case, if you wish, you will be given the package leaflet for both drugs.

Voluntary participation and withdrawal

You are free to decide whether or not you wish to take part in this study, participation is entirely voluntary. If you decide to participate, you still have the possibility to withdraw at any time, without having to give any explanation, and without any penalty or negative consequences for you. If you change your mind about your data, you have the right to request its destruction or anonymisation, through your doctor/researcher. However, you should be aware that the data obtained in the analyses carried out up to that point may be used for the purposes requested and may be retained in compliance with the corresponding legal obligations.

Potential benefits

No direct benefit is expected from your participation in the study. However, the information obtained from this research project may contribute to medical progress and could help other patients in the future. ´will not receive any financial benefit from the donation of the samples and the transfer of the data provided, nor will´ have any rights to any commercial benefits from the discoveries that may be made as a result of the research carried out.

Alternative treatments
If you do not participate in the study, you will be treated according to standard clinical practice.

Data protection and confidentiality
All information about your results will be treated in the strictest confidence. Both the centre, the promoter and the research team are responsible for the processing of your data and undertake to comply with the data protection regulations in force, currently Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of digital rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (RGPD). The data collected for the study will be identified by a code, so that no information that can identify you is included, and only the research team will be able to relate this data to you. ,
their identity shall not be´ disclosed to any other person except to the health authorities, when requested to do so by´or in cases of medical urgency. The Research Ethics Committees, the Research Ethics Committee, the
representatives of inspecting Health Authority and personnel authorised by the Sponsor may only have access to check personal data, clinical trial procedures and compliance with the standards of good clinical practice (while maintaining the confidentiality of the information).
Your data will be kept under appropriate security conditions and it is ensured that subjects cannot be identified through means considered reasonable by persons other than those authorised. The research team will analyse your data based on the legitimate interest of achieving the purposes of the study. The Investigator and the Sponsor are obliged to retain the data collected for the study for at least 25 years after completion of the study. Thereafter, your personal information will only be retained by the facility for your health care and by the research team for other scientific research purposes if you have given your consent to do so and if permitted by applicable law and ethical requirements.

If the results of the study are likely to be published in scientific journals, no personal data of the participants in this research will be provided at any time. We inform you that you have the right to access, rectify or cancel your data, and you may limit the processing of data that are incorrect, request a copy or that the data you have provided for the study be transferred to a third party. To exercise your rights, or in the event that the participant wishes further information on the processing of your personal data, you may contact the principal investigator of the study whose details are specified at the end of this document, the Data Protection Officer of the Regional Health Authority (dpd@saludcastillayleon.es) or our centre (protecciondedatos@ibsal.es). We remind you that the data cannot be deleted, even if you stop participating in the trial in order to ensure the validity of the research and to comply with legal obligations. You also have the right to contact the Data Protection Agency if you are not satisfied.

Information on results
At your request, at the end of the study and in accordance with article 27 of Law 14/2007 on Biomedical Research, you may be provided with information on the results of this research work.

I consent to the future use of the data collected in this research study for further research related to the medical specialty or research area of this study.

□ **YES** □ **NO**

I consent to future re-accessing of my medical records to collect data deemed important for further research related to the medical specialty or research area of this study.

□ **YES** □ **NO**

Contact details of the research team:

If you have any questions or need further information, please contact: Name:
Telephone:

your decision, both the promoter and the research team would like to thank you for your time and attention.

INFORMED CONSENT

Title:	**Randomised clinical trial to evaluate the dose and time of administration of indocyanine green in near-infrared fluorescein cholangiography during cholecystectomy. laparoscopic:**
Code:	**DOTIG study.**

I *(Name and Surname*_____

I have read the information sheet I have been given about the study. I

have been able to ask questions about the study.

I have received sufficient information about the study.

I have read the information sheet provided to me.

I have spoken to the Investigator _____

I understand that my participation is voluntary. I

understand that I may withdraw from the study:

1st Whenever you want

2nd Without having to give explanations

3º Without having any negative repercussions

I voluntarily agree to participate in the clinical trial and consent to the use of all information obtained. I understand that I will receive a signed copy of this informed consent form.

_____

Participant's signature Date

_____

Name and signature of the researcher Date

_____

Signature of the legal representative, family member or de facto related person Date

INFORMED ORAL CONSENT IN THE PRESENCE OF WITNESSES

Title:	**Randomised clinical trial to evaluate the dose and time of administration of indocyanine green in near-infrared fluorescein cholangiography during cholecystectomy. laparoscopic:**
Code:	**DOTIG Studio**

I *(Name and Surname*_____

As a witness, I affirm that in my presence I have been informed to:

MR/MS _____

- You have been read the information sheet you have been given about the study.
- You have been able to ask questions about the study.
- You have received sufficient information about the study.
- You have spoken to the _____

You understand that your participation is voluntary. You

understand that you may withdraw from the study:

1º Whenever you want

2º Without having to explain

3º Without any negative impact

You voluntarily agree to participate in the clinical trial and consent to the use of all information obtained. You understand that you will receive a signed copy of this informed consent form.

_____ _____

Signature of witness Date
(Date in handwriting of the witness)

_____ _____

Name and signature of the researcher Date