**INFORMED CONSENT FORM**

| | |
|---|---|
| Title of the study: | **Near Infrared Transcranial Laser Therapy in Subjects with Major Depressive Disorder: A study of Dosing with Laser** |
| Sponsor | Pthera LLC |
| Representative | Peruvian Clinical Research S.A.C. |
| Principal Investigator | |
| Name of Institution<br>Research Center<br>Research Center Registration (RCI) | Vesalius Clinic<br>Clinical Research Center in Psychiatry, RCI - 591 |
| Address of the center | Calle Jr. Joseph Thompson 140, San Borja 15036 |
| Phone | 996429732 |
| Principal Investigator's E-mail | bmacciotta@yahoo.com |
| Ethics Committee | Via Libre's Institutional Bioethics Committee |
| Health Authority | National Institute of Health |
| Participant Initials | |
| Participant Identification Number | |

**DEAR PARTICIPANT:**

We are inviting you to participate in a research study on major depressive disorder, because you have this condition and we want to investigate how good a laser treatment can be in order to treat your condition in a timely manner and help people like you to alleviate mainly the symptoms associated with this condition.

The treatment you will receive with this medical device has been previously tested on other people and has been proven useful and safe in different types of studies and in different diseases. However, in this model of medical device called EXPi [through which the near infrared transcranial laser therapy (NIR-TLT) will be administered to you] is under investigation for the disease you have.

Therefore, you were chosen to participate in the study because you have a major depressive disorder and meet the inclusion criteria mentioned in the study. You were informed in the study.

**Your participation is completely voluntary and you may withdraw from the study at any time and will have no consequences for your usual or future treatment at your health care facility.** You can also ask your doctor if you have any questions and you can also request more information from the Principal Investigator.

**OBJECTIVES OF THIS CLINICAL TRIAL**

Major depressive disorder is becoming more and more frequent in our country. In our reality there is a great variety of treatments for these problems, but many of them are not for sale in the market.

The present product has been tested in free as well as in other realities due to several problems such as the lack of studies that strengthen its safety at the population level in specific geographic regions where the effect of the treatments may be affected by genetic or cultural factors. For this reason, it is pertinent to evaluate this product, confirming its safety. There are no national studies (with Peruvian population) on the efficacy and safety of the use of near infrared transcranial laser therapy (NIR-TLT), also in the same population the safety profile of the use of the LiteCure EXPi (investigational device for the delivery of laser therapy) for the treatment of major depression is not known. The study doctor will perform an evaluation and diagnosis and assign you a specific treatment of the study treatment, which will be covered by the present research work.

Therefore, determining the efficacy and safety profile (meaning how many adverse events occurred during the study) of this product is not only important but will also contribute to the current body of literature on the product (i.e. general information about this therapy). This study will be conducted in order to know how useful (effective) the product "EXPi medical device" is in reducing the symptoms of your disease and to know the possible adverse events evaluated.

**STUDY TREATMENTS**

The treatment we want to evaluate called Near Infrared Transcranial Laser Therapy (NIR-TLT)® wants to compare the effect(s) of each of the four doses of NIR-TLT on the symptomatology of depression: antidepressant effect. We also hope to be able to estimate the effect size of the antidepressant action as a function of the irradiation applied to the skin of NIR-TLT being the most effective dose and to compare the safety and tolerability at each dose.

Near Infrared Light is a non-ionizing electromagnetic wave, is invisible, penetrates the skin and skull into the brain tissue, is non-invasive, dissipates minimally as thermal energy and is absorbed primarily by specific chromophores. The benefits of this treatment are wavelength specific. You will be assigned to receive one of the 4 doses of NIR-TLT. Neither you nor your doctor will know which treatment you will receive.

In this study neither you nor the doctor will know which of the four treatments you are receiving so that your treatment is given without any interruption or error. This process is called "blinding".

Other treatments (mainly antidepressant medications) are available for use when you are diagnosed with your condition, both individually and in associations. You are not required to agree to receive the treatments proposed in this study and it is up to you to decide whether or not to participate in the treatments offered in this study.

**WHAT IS KNOWN ABOUT THE SUBJECT UNDER INVESTIGATION? HAVE OTHER SIMILAR STUDIES BEEN CONDUCTED PREVIOUSLY?**

There are no national studies (Peruvian population) on the efficacy of NIR-TLT with the use of the LiteCure EXPi laser. However, in other countries efficacy and safety studies of this therapy have been carried out with another model of the device for different diseases such as neuropathic pain, osteoarthritis, muscle injuries, traumatic brain injuries, etc.

## IF YOU AGREE TO PARTICIPATE, WHAT SHOULD YOU DO (EXPLAIN THE PROCEDURES RELEVANT TO YOUR PARTICIPATION)?

Before the study starts, the principal investigator will need to perform some tests. Most of these tests are part of your regular medical care and can be performed even if you do not participate in the study. If you agree to participate, you will agree to follow the instructions and treatment that the study doctor prescribes, as well as to participate in the following visits:

### Visit 0 (Day 1, start of the selection period)

If you meet the screening criteria for this study, the purpose and details of the study will be explained to you and, if you wish to participate in the study, you will be asked to sign this written informed consent prior to any procedures related to this study. The study doctor will obtain your demographic information (date of birth, race), medical and surgical history, as well as your medication history, current gastrointestinal and systemic disorders.

The following evaluations/activities will be conducted:

- Physical examination.
- Vital signs.
- Treatments currently used.
- See if it meets the study's selection criteria.
- Blood and urine samples will be taken
- Several Mental Health questionnaires will be completed by both you and your doctor.

The amount of blood to be drawn at this visit will be 15 ml (approximately 3 tablespoons). Drawing blood may cause pain and less likely bleeding, bruising or swelling at the puncture site and, in rare cases, may cause dizziness and fainting.

There is a possibility that you may randomly enter a subgroup of the study. Participants who enter this subgroup will receive the same treatment as the others, according to the protocol instructions. The difference is that the people in these groups will undergo an imaging study called PET. It is a type of tomography that will show us how your brain works before and after receiving the laser. Therefore, if you fall into this group, you should go for a PET scan before starting therapy and within 24 hours after the last dose of treatment. The travel and cost of the study will be covered by the sponsor and will not be an expense to you.

### Treatment Period (Visits 1 to 18)

The study doctor will perform a final review of the inclusion and exclusion criteria. If you meet the criteria requested by the study, you will be randomly assigned one of the four study treatments (equivalent to flipping a coin and determining whether it is heads or tails) and the treatment will be explained to you according to the group to which you belong according to the established assignment scheme.

Treatment will be given at the visits assigned for each treatment according to the treatment arm indicated by the treating doctor.

**Visits:**

Once the treatment visit schedule is initiated, about 18 visits must be completed to complete the treatment. At some visits (1, 9 and 18) you will have additional evaluations such as two EEGs at each visit (which lasts 10 minutes before treatment and 10 minutes after treatment) and 4 mental evaluation questionnaires.

You must agree to comply with all visits scheduled in this study. If you miss a visit, you must contact the investigator immediately and the investigator will determine whether or not it is possible to reschedule this visit. If the visit is missed and cannot be rescheduled within 48-72 hours you will be withdrawn from the study.

**Final visit (post treatment - week 8)**

The following evaluations/activities will be conducted:

- Vital signs.
- Evaluate concomitant treatments.
- Evaluate adverse reactions.
- Mental Health Questionnaires completed by both you and your doctor.

It is very likely that you will not have any risk or discomfort in any of the procedures mentioned above, but you should know that if you have any discomfort, please inform the study investigator.

If you present any adverse event considered of serious intensity, you will be withdrawn from the study.

Remember that, if you enter the study subgroup, you must go for a PET study within 24 hours after the last dose of treatment. The travel and cost of the study will be assumed by the sponsor and will not be an expense for you.

## HOW LONG WILL THE STUDY LAST? HOW MANY PEOPLE WILL PARTICIPATE?

The duration of the study will be until completing the total number of participants needed for the objective of this study. The duration of the treatment will be a maximum of 06 weeks, where you will receive 3 NIR-TLT sessions per week during this time, and a follow-up evaluation of 02 weeks after the end of the treatment. Likewise, you will visit your doctor's office according to the schedule of visits assigned to each arm of the study.

A minimum of 112 participants will participate, 28 for each assigned treatment.

## EXPENSES FOR PARTICIPATION IN THE STUDY

This clinical study is sponsored by Pthera LLC, a company dedicated to the production of laser therapy medical supplies that will facilitate the study treatment so that participation will be free of charge to you as a patient. Participation in this study, including visits to the center, study treatment or rescue therapy, will not result in any monetary expense to you or your health program.

In addition, the sponsor has made arrangements with the study investigator to reimburse you for reasonable travel and refreshment expenses that you may incur as a result of your participation in this study. This reimbursement will be S/. 15.00 Nuevos Soles for each completed visit, without the need for you to submit any proof of your expenses. Whenever these costs are higher than this amount and, in order to protect the rights of the participants, the amount will be reimbursed taking into account the personal and specific considerations of each of these expenses.

The costs of conducting this study will also be paid to the research center, and the principal investigator will receive remuneration for conducting the study. In the event that you are randomly assigned to the study subgroup, the travel and cost of the PET study will be borne by the sponsor and will not be an expense to you.

**WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?**

You may not experience any direct health benefits and your condition may not improve or may even worsen while participating in this research study, just as it would during routine treatment outside of a clinical trial. There is a possibility that you may experience some discomfort as a result of treatment with any of the treatments in this study. Among those we note:

Based on human clinical trial experience to date with NIR-TLT, the following are the most frequently reported adverse events:

1. Erythema at the application site
2. Pain at the application site
3. Discomfort at the application site
4. Heat at the application site
5. Headache

Additional possible mild side effects of NIR-TLT documented:

1. See bright colors, abnormal taste
2. Feeling "out-of-body" experiences
3. Insomnia, restless sleep, erratic sleep, early morning awakening.
4. Vivid dreams
5. Irritability
6. Difficulty finding words
7. Abdominal distention

Among the less frequent are the risks of worsening depression, suicide and manic change.

For this reason, the doctor will be in close contact with you throughout the study and should you experience any discomfort during the treatment period.

We hope that you will follow the medical indications in the use of the treatments we are evaluating. In any case, the results of this study will help to provide better treatment for other patients with this indication in the future.

Although the risk of injury is extremely low, in the event of an injury related to the use of the treatments in this study, Pthera LLC will provide free medical treatment whenever it is related to the use of the treatments in this study and is required. In the event of a trial-related injury or death, Pthera LLC, or its designee, will provide financial compensation for the injury or death. The person you designate has the right to contact the sponsor or its representative to claim compensation in the event of death. The sponsor works with an insurance company and has an insurance policy to cover injuries related to the clinical trial. In order for this policy to apply you will need to follow all instructions and advice of the principal investigator. You will not be responsible for any of the costs of this treatment.

Performing the PET scan on participants who are chosen for it involves radiation exposure. A whole body PET scan exposes you to approximately 8 mSv of radiation. It has been established that a person can receive up to 20 mSv per year. On the other hand, having a PET scan is equivalent to having 2.5 CT scans, which are commonly performed. This does not imply a risk for you or your family. It is a safe procedure.(1-5)

In the event that you have an unfavorable evolution of the study treatment, you will be evaluated for medical care. This decision will be made within 24 hours of being in the study; therefore, if you feel that you are not improving or are getting worse, please contact the study doctor immediately.

If you present any adverse event considered of serious intensity, you will be withdrawn from the study.

**WHAT BENEFITS WILL I HAVE IF I PARTICIPATE IN THE STUDY?**

You may or may not benefit from the treatment being studied. Your medical condition may improve, stay the same or even get worse with the treatment under study.

You may have benefits for your treatment because the literature mentions that this treatment is effective and safe for the treatment of your disease.

Likewise, the information obtained from this study will serve to provide greater support for this treatment in the general Peruvian population suffering from this type of disease.

1. Radiation protection of patients during PET/CT scanning [Internet]. IAEA; 2017 [cited Nov 4, 2021]. Available from: https://www.iaea.org/resources/rpop/health-professionals/nuclear-medicine/pet-ct/patients. 2. Information for Radiation Workers [Internet]. NRC Web. [cited 2021 Nov. 4, 2021]. Available from: https://www.nrc.gov/about-nrc/radiation/health-effects/info.html. Table 1 Recommended dose limits in planned exposure situations (ICRP... [Internet]. [Internet]. ResearchGate. [cited 2021 Nov 4, 2021]. Available from: https://www.researchgate.net/figure/Recommended-dose-limits-in-planned-exposure-situations-ICRP-Publication-103_tbl1_221798681. 4. Whole-Body PET/CT Scanning: Estimation of Radiation Dose and Cancer Risk | Radiology [Internet]. [cited 2021 Nov 4, 2021]. Available from: https://pubs.rsna.org/doi/10.1148/radiol.2511081300. Table 2 Occupational radiation safety limits (Walsh et al. 2008) [Internet]. ResearchGate. [cited 4 Nov. 2021]. Available from: https://www.researchgate.net/figure/Occupational-radiation-safety-limits-Walsh-et-al- 2008_tbl2_300920240.

**HOW WILL YOU KEEP MY PERSONAL DATA CONFIDENTIAL? HOW WILL YOU ENSURE THAT YOUR IDENTITY IS NOT KNOWN?**

Medical results and personal information are collected and documented during any treatment. The data collected for this clinical study will first be recorded in your doctor's medical records or other original documents, e.g. laboratory reports, as any other medical results. The data relevant to the study will subsequently be transferred to a data collection notebook that will not bear your name or address. The data will be documented in these notebooks anonymously, i.e. with a code consisting of a study number, sex and the month and date of birth, which will be unambiguous. You will have to give your consent for the anonymized recording of your personal data and the subsequent transfer of this data to the Sponsor, to the competent authorities including the Peruvian National Institute of Health, Research Ethics Committees, etc. Without your consent for this form of documentation, transfer and evaluation of your data you cannot participate in this clinical study. You may withdraw from the clinical study at any time, but you must give your consent for the data collected up to that point to continue to be used (anonymously). Your data may be needed to evaluate the effects of the treatment, to protect your interests (e.g. in case of an insurance claim) or to comply with legislation, e.g. archiving of study data for the treatment registry. Even if you prematurely stop participating in this clinical study, you should be aware that the data already collected will be transferred in anonymized form to the above-mentioned agencies. To confirm the accuracy and completeness of the data documented in the special clinical trial data collection notebooks, your medical records may be inspected by regulatory authorities, ethics committees or the Sponsor's qualified and specifically authorized persons, so-called clinical monitors or auditors. These individuals are bound by confidentiality. By your consent to participate in this clinical trial, you release your doctor from liability for discretion as he/she makes your medical records available to authorized persons for inspection purposes. In the event that the results of this study are published in medical journals or presented at medical conferences, your identity will not be disclosed. In addition, the forms containing your identification data will be stored in a location designated by the principal investigator that will have a key to ensure that no other person has access to them. Likewise, the database that will be created will avoid having identification data, this data will be stored in another list that the principal investigator manages for contact in case of an adverse reaction or to schedule follow-up calls required by the protocol.

The owner of the personal data (i.e. you) has the right to exercise the right of access to such data free of charge at intervals of no less than six months.

Information about the results of the study may be published in scientific congresses, scientific journals and the researchers may keep you informed of the results once they are analyzed and published openly to the community.

In addition, a description of this clinical trial will be published on the website of the Peruvian Clinical Trials Registry (REPEC): https://ensayosclinicos-repec.ins.gob.pe/. This web site will not contain any information that will allow your identification as a participant, this page is of public use and domain and free of charge.

## CAN I STOP PARTICIPATING AT ANY TIME, EVEN AFTER I HAVE ACCEPTED?

You are free to withdraw your consent to participate in the research at any time without prejudice to your subsequent medical care; you should simply notify the investigator of your decision orally or at visits to you.
After you withdraw your consent, your health information will no longer be collected, but all previously collected information will be used.

## IF YOU ARE PREGNANT OR BREASTFEEDING, CAN YOU PARTICIPATE?

It is very important that a woman is not pregnant or breastfeeding, because the treatments are not recommended for use at these stages. If you are pregnant or suspect you are pregnant, you will not be able to participate in this study. There are insufficient studies on teratogenic and carcinogenic effects in humans.

It is mandatory that you use contraception during the study treatment (08 weeks) if you decide to have sexual intercourse. A double barrier contraceptive method (condom and spermicide) will be given to you free of charge in case you confirm that you have sexual intercourse.

Also, during the first visit, we will perform a urine pregnancy test to confirm whether or not you are pregnant.

If you become pregnant during your participation in the study, you will be withdrawn from the study and referred to a gynecologist so that you can have a strict control of your pregnancy. Likewise, the newborn will be monitored until 6 months after birth.

## VOLUNTARY NATURE OF PARTICIPATION AND WITHDRAWAL

It is important that you understand that your participation in the clinical trial is voluntary. If you do not want to participate, you are not obligated to do so. You are free to withdraw from this study at any time without impacting your routine medical treatment or relationship with your doctor or hospital. If you would like to withdraw, please contact your doctor first. You should request any information you wish before signing the informed consent document. Your doctor may discontinue this study treatment at any time if it appears to be in your best interest (e.g., your health condition worsens or if you experience too many adverse reactions), or if your compliance with the study requirements is not satisfactory (e.g., irregular application of treatments, irregular visits to your doctor). The decision to discontinue the entire study prematurely is the Sponsor's decision. If there is a direct risk, the Trial Sponsor and participating doctors will immediately take appropriate measures to avoid injury.

## INSURANCE

Although you are being asked to participate in a clinical study in which serious risks are highly unlikely, an impact on your health can never be completely ruled out. As a participant in this study, you will be covered by insurance as stipulated by law and in accordance with the insurance conditions in the event of injury resulting in death or damage to health as a result of procedures performed during the research study.

The sponsor company of the clinical trial has contracted an insurance company called **PACIFICO COMPAÑÍA DE SEGUROS,** applying for clinical research insurance, which applies for the entire duration of the trial. In order to ensure that everything is clear, for the duration of the clinical trial, should any damage to your health occur, you are obliged to undergo any further medical treatment only after consulting your doctor (unless it is an emergency, in which case you must inform your doctor immediately). You are also obliged to notify your doctor and insurance company immediately of any possible damage to your health. Deliberate or grossly negligent breach of the insurance obligation may result in loss of insurance coverage.

On the other hand, if your health problem is not a direct result of the treatment or procedures in this study, you or your insurance will bear the cost of this care through the mechanisms that would normally operate in these circumstances.

**NEW INFORMATION THAT ARISES DURING THE STUDY**

If during the study there is new information that may be important enough that you may want to stop participating (for example, if several participants have an unexpected adverse reaction that may be of concern to you), you will be informed as soon as possible. If you agree to continue in the study, you will be asked to sign an updated consent form.

At the end of the study, the principal investigator will contact you by telephone to inform you of the results of the study, which will be formally delivered in a document. If the principal investigator decides not to give you this information, it is most likely because the sponsor has informed you that the data will remain confidential.

The sponsor agrees to provide you with all current information about the investigational product or investigational procedures, even though it may affect your willingness to continue in the study.

If during this study you or any of your family members have any questions regarding this research, or if you should experience any medical problems, please call any of the following telephone numbers:

- Name of Principal Investigator: Dr. Beatrice Macciotta
- Address: Calle Jr. Joseph Thompson 140, San Borja 15036
- Daytime phone number(s): 996429732
- 24-hour phone number(s): 996429732
- E-mail address: bmacciotta@yahoo.com

**WHAT WILL HAPPEN WHEN THE STUDY IS COMPLETED?**

The purpose of this study is to support the safety and efficacy of the NIR-TLT product requested by the National Treatment Authority (ANM).

At the end of your participation in the study, an evaluation of all study participants will be made and a medical report will be issued, which will be submitted to the Ministry of Health for authorization to sell this product in pharmacies.

**QUESTIONS ABOUT YOUR RIGHTS AS A PARTICIPANT AS A PARTICIPANT:**

You may ask questions about this consent form or about the study (before you decide to participate or at any time during the study).

Please contact your doctor or the study staff with any questions or concerns you may have. Their telephone number is printed on the first page of this form.

If you have any questions about your rights as a participant or about the ethics of the study, you may contact **Dr. María Luisa Cairampoma Gago**, President of the Institutional Bioethics Committee (IBC) of VÍA LIBRE, by phone at 203-9900 from Monday to Friday from 9 a.m. to 6 p.m. or at Jr. Paraguay 478 - 486, Cercado de Lima and by e-mail: comitebioetica@vialibre.org.pe.

An Ethics Committee is made up of a group of people from scientific and non-scientific backgrounds who conduct an initial and ongoing review of the research study to maintain safety and protect the rights of participants.

When you consider that your rights have been violated or in case of any complaint, you may contact the National Health Institute (Dirección de Investigación e Innovación en Salud - DIIS), the regulatory entity for clinical trials, through the following telephone numbers: 748-0000 and 748-1111 annex 2191; or by written communication through the following e-mail: consultaensayos@ins.gob.pe; or through a formal document presented through the institution's physical or virtual desk; or go in person to the DIIS facilities at the INS at the following address: Av. Defensores del Morro 2268 (Ex Huaylas) - Chorrillos, Lima 9.

Additionally, you will find information on the INS website https://ensayosclinicos- repec.ins.gob.pe/.

**WHAT ARE YOUR RESPONSIBILITIES IF YOU PARTICIPATE IN THIS STUDY**?

If you agree to participate in the study, you are expected to:

- Keep study appointments. If you are unable to keep an appointment, contact the PRINCIPAL INVESTIGATOR or research study staff to reschedule as soon as you know you will not be able to.
- Inform the Principal Investigator or research study staff of any changes that occur in your health during the study.
- Inform the Principal Investigator or study staff of any changes to your treatments during the study.
- While you are participating in this study, you must not participate in any other project without the approval of the Principal Investigator.
- Inform the study doctor or research study staff if you change your mind about staying in the study.
- Inform your primary care doctor of the study treatment in which you are participating.

**Consent:**
By signing this document, I indicate that I understand the following:

I understand the objectives of the study and the procedures to be carried out. In addition, all my doubts have been answered.
I agree to voluntarily participate in this study and may withdraw at any time from the study. I have been informed of all my rights and I am not waiving any of them.
I will receive a copy of this signed and dated informed consent document.

In addition to agreeing to the initial recruitment interviews, I agree to:

| **YES or NO in the following activities: (Mark with an (X) as appropriate)** | | |
|---|---|---|
| Answer questions about background, medical history, etc. | YES | NO |
| To be contacted by study personnel by telephone to learn about the evolution of my symptoms. | YES | NO |
| I allow you to store my identification data, health information and contact information in physical and electronic files. | YES | NO |
| I give my consent to the proposed procedure and I know my right to withdraw it whenever I wish, with the only obligation to inform the doctor responsible for the study of my decision. | YES | NO |

**By signing, I agree to authorize the provisions of this document:**

| PARTICIPANT | | | |
|---|---|---|---|
| Name and Surname<br>Identity Card | Signature | Date | Time |
| | | | |

| LEADS THE CONSENT | | | |
|---|---|---|---|
| Name and Surname<br>Identity Card | Signature | Date | Time |
| | | | |

The study subject has indicated that he/she is unable to read. A study staff member has read the consent document to the subject and has discussed this consent document with the subject and has been given the opportunity to ask questions of the study staff.

Name and surname of the impartial witness, identity document, date and time.

| Name and Surname | Signature | Identity Card | Date |
|---|---|---|---|
| | | | |

*Impartial Witness: A person independent of the trial who cannot be influenced by persons participating in the trial and who attends the informed consent process if the subject or the subject's authorized representative is unable to read, and who reads the informed consent and any other written information to the subject.