INFORMED CONSENT FORM

"MODULATION OF NEURONAL CONNETTIVITY ALONG THE VISUAL PATHWAYS IN PATIENTS AFFECTED BY GLAUCOMA THROUG TREATMENT WITH CITICOLINE ORAL SOLUTION: MULTIMODAL MORPHO-FUNCIONAL STUDY"

Promotor centre: IRCCS-Fondazione GB Bietti

Principal Investigator: Prof. Vincenzo Parisi

Address: IRCCS Fondazione G.B.Bietti – Presidio Britannico, Via di Santo Stefano Rotondo 6, Rome

Name of Patient

_____

Dear Patient,

You are invited to voluntarily participate in this clinical study. Your participation is able to improve knowledge about glaucoma and new diagnostic approaches.

You will receive a copy of this information sheet to read it and have the opportunity to inquire about the details of the study and decide whether or not to participate in the clinical trial.

If you decide to participate in this study, you must date and sign this document, as well as the doctor who conducted the discussion to informed consent. A signed copy will be given to you.

This information sheet will describe how the study will take place and what your role will be within it, if you decide to participate. The Clinician in charge of the study will answer any questions you wish to ask about the study, or about this Consent Information Form. It is your right to read the form carefully and ask any questions you wish about the information contained therein.

GENERAL INFORMATION AND PURPOSE OF THE CLINICAL STUDY

You were selected to participate in this clinical trial because you have glaucoma.

Glaucoma is a chronic-degenerative disease that affects the nerve fibers that make up the optic nerve, that is, the nerve that transmits visual information directly from the eye to the brain, resulting in damage to the visual field.

The most common form, primary open-angle glaucoma, has as its main risk factor the increase in intraocular pressure for which the first therapeutic approach is represented by hypotonizing topical drugs. However, given that more than one third of patients under good pressure control delay, but do not arrest the progression of visual impairment, other non-pressure dependent mechanisms are thought to be involved.

Glaucomatous visual impairment can be assessed by examining the visual field (VF).

The morphological damage that develops in glaucoma of the retinal ganglion cells (RGCs) that give rise to the optic nerve and of the optic nerve fibers (RNFL) can be detected, in a non-invasive way, through the use of Optical Coherence Tomography (OCT).

The functional damage is instead detected through current electrophysiology techniques, which allow to quantify in a specific and differentiated way the dysfunctions of the various elements that form the optical pathway. In particular, through the ERG from Pattern (PERG) or the PhNR it is possible to quantify the functionality of the RGCs, while the nerve conduction along the optical pathways is objectivable through the recording of the Visual Evoked Potentials (VEP). Through the simultaneous recording of PERG and VEP it is possible to derive an electrophysiological index of nerve conduction dysfunction between the eye and the brain: Retino-Cortical Time (RCT).

Through the evaluation of the RCT, it has been hypothesized that in glaucoma the perimetric deficit is the result of two types of dysfunction: one directly at the ocular level (specifically related to RGCs) linked to the reduction of the transmission of the nerve impulse that comes from the retina towards brain structures.

Thanks to the use of modern neuro-imaging techniques (Magnetic Resonance), it has been shown that glaucoma patients can present structural anomalies not only in the retinal cells, but also in the structures that form the optical pathways, that is that part of the brain which carries visual information from the eye to the occipital cerebral cortex.

In glaucoma patients it has been observed that Citicoline, an endogenous substance that is already produced by the human body, which, in this study, will be administered through a food intended for special medical purposes (taken by mouth), is able to increase the functionality ("neuropotentiation") of the retinal nerve cells and the optic nerve, to prevent the progression of the degenerative processes of the retinal nerve cells ("neuroprotection") thus reducing the progression of the perimetric deficit.

The aim of the present research will be to evaluate the effects of Citicoline in oral solution on nerve conduction along the optic pathways in glaucoma patients, and whether or not these effects occur concurrently or not with structural changes in RGCs and RNFLs or changes in structures. nerve pathways that form the optic pathways.

Type of study

The study in question involves a treatment with administration of Citicoline in oral solution or Placebo. It is a prospective study (i.e. in which the people involved are followed from the beginning of the study to its conclusion), multicenter (involving more than one center / institute), double-blind (i.e. in which the participants and investigators, I am not aware of the patient group).

It provides for the enrollment, over 12 months, of 60 patients with open-angle glaucoma.

Patients selected according to the inclusion / exclusion criteria, after signing the informed consent, will be randomized into two groups:

a) In a group of patients (30 patients) with glaucoma. Citicoline will be administered in oral solution (10 ml / day, Neurotidine®) for 12 months

b) another group of patients (30 patients) with glaucoma will be given Placebo (Containing all the excipients of Neurotidine ®) (10 ml / day) for 12 months

Participation in the study

If you decide to participate in the study, you will undergo an eye examination (screening visit T0) to verify if you have the clinical characteristics to participate in the study, as well as some clinical and instrumental evaluations as specified below (complete eye examination, examination of the VF, VEP, PERG and OCT.

Once the eligibility to participate has been ascertained, he will undergo another visit (Basal view T1) in which the tests carried out at T0 will be repeated with the addition of MRI.

At the end of this visit you will be assigned to the group of patients treated with Citicoline or treated with Placebo; the assignment to one or the other group will take place in sequential order of presentation of the patient (with a 1: 1 probability of joining one or the other group) in order to constitute two homogeneous groups in number.

At the end of the T1 visit, you will be given 4 bottles containing 500 ml Neurotidine ® or Placebo and you will be given the relative instructions for administration. The regimen will be 1 administration of 10 ml once a day for 6 months. Each bottle can be used for 50 days.

The follow-up will be carried out:

1) After 6 months (T2): a complete eye examination will be performed including the following assessments: corrected visual acuity, biomicroscopy, indirect ophthalmoscopy, intraocular pressure measurement with Goldmann applanation tonometer, VF test, recording of PERGs and VEPs, imaging of the optic nerve and retinal nerve fiber layer by OCT.

At the end of this visit you will return the bottles delivered for the evaluation of the correct consumption of the treatment assigned to you.

If there are no variations with respect to the inclusion / exclusion criteria, and you have made correct use (ie you have assumed more than 80%) of the assigned treatment, you will continue the study for a further 6 months. In this case, you will be given 4 bottles containing 500 ml Neurotidine ® or Placebo and you will be given the relative instructions for administration. The regimen will be 1 administration of 10 ml once a day for 6 months. Each bottle can be used for 50 days.

2) After 12 months (T3): a complete eye examination will be performed including the following assessments: corrected visual acuity, biomicroscopy, indirect ophthalmoscopy, intraocular pressure measurement with Goldmann applanation tonometer, visual field test, recording of PERGs and VEP, imaging of the optic nerve and retinal nerve fiber layer by OCT.
The MRI will also be repeated.

At the end of this visit you will return the bottles delivered for the evaluation of the correct consumption of the treatment assigned to you.

The clinical and instrumental tests you will undergo are as follows:

- Eye examination

The eye examination consists of the measurement of visual acuity and observation of the anterior ocular structures (cornea, lens, iris) and posterior (retina, vitreous and optic nerve). Observation of the back of the eye requires ocular mydriasis or the transient pharmacological dilation of the pupil (obtained through the instillation of eye drops). The eye examination also includes the measurement of intraocular pressure (carried out through the use of an instrument - tonometer - placed on the surface of the eye) which takes place after instillation of superficial anesthetic eye drops.

- Measurement of visual acuity

The visual acuity (AV) examination will be evaluated to define the best optical correction with or without trial lenses for far and near.

- Computerized visual field

An automated VF examination will be performed by means of which the portion of the visual field perceived or not perceived by you will be estimated by measuring the retinal sensitivity indices and using parameters that evaluate the reliability of the answers given.

- Electrophysiological examinations

PERG is a clinical diagnostic technique that allows recording of the retinal bioelectric response following structured stimulation on a monitor. It involves the application of electrodes to the skin of the eyelids and forehead. The VEPs record the conduction times of the optic nerve along the optic pathway from the eye to the region of the brain responsible for coding the images.

- Optical Coherence Tomography (OCT)

It is an instrumental examination that allows the measurement of the morphology and the thickness of the retina and of the nerve fibers forming the optic nerve.

- Neuroradiological evaluation

It is a set of magnetic resonance techniques that allow you to measure the integrity of the micro- and macroscopic structure of the internal areas of the brain responsible for visual function, such as the thalamus, as well as the cerebral gray matter. Furthermore, these tests allow to evaluate the strength of the connection between different brain areas.

To perform some tests (OCT and eye examination with fundus visualization), it may be necessary to instill mydriatic eye drops (which dilate the pupil and temporarily blur near vision). It may also be necessary to instill anesthetic eye drops to measure eye pressure which is part of the eye examination.

No tests that you will be required to take to participate in this study are invasive (i.e. they cannot harm ocular structures and general health) and do not require the administration of any contrast medium.

During the entire duration of the study (both at the baseline visit and at the 6 and 12 month visit), all the clinical and instrumental evaluations foreseen by the study (eye examination, measurement of visual acuity, VF, electrophysiological and OCT examinations) will be carried out, as stated, by "evaluator" investigators who will not know whether the patient examined belongs to the group of patients treated with Citicoline or to the group of patients treated with Placebo.

All the instrumental examinations related to the study will be carried out at the Glaucoma and Neurophysiology of Vision and Neuropphysiology Unit at the British Presidium, Via di Santo Stefano Rotondo 6, Rome, with the exception of the MRI examination which will be carried out at the Nuova Clinica Latina. From Rome.

The study was promoted by the IRCCS-GB Bietti Foundation.

The study was notified to the IRCCS Central Ethics Committee, IFO / Bietti Section in order to ensure the protection of the rights, safety and well-being of the participants in this clinical study and to provide a public guarantee of such protection.

This study is conducted according to the guidelines for good clinical practice (ICH / GCP) and according to the most recent version of the Declaration of Helsinki developed to protect people participating in clinical trials.

POSSIBLE RISKS

Possible risks deriving from food for special medical purposes

Neurotidine®, used in the present study, is a food supplement based on Citicoline for which there is no evidence describing potential side effects and / or specific contraindications; the only warnings are not to take it during pregnancy and breastfeeding, as the possible effects on the fetus and / or newborn are not fully known.

For this reason, pregnant or lactating women cannot participate in the study; at the same time, women of childbearing potential must consent to the use of adequate contraceptive methods for the entire duration of treatment with Citicoline provided for in the study; For the safety of patients, it is noted that scientifically accepted methods of birth control do not provide absolute protection: some women have become pregnant even with the regular use of these types of methods.

Possible risks deriving from the procedures envisaged by the study

All the assessments provided for in this study are non-invasive tests, normally performed in clinical practice, which do not involve side effects but only possible inconveniences and / or annoyances.

The execution of PERG and VEP involves recording the bioelectric activity of the retina and of the optic nerve (without any type of stimulation of an active electrical nature) through the application of electrodes on the skin of the eyelids, forehead and scalp, therefore risks relating to the procedure are conceivable.

The eye drops used to dilate the pupil for the execution of the eye examination and for the acquisition of the OCT exam could cause some transient effect and / or discomfort such as a transient conjunctival hyperaemia (redness of the conjunctiva or the external part of the eye), photophobia (transient aversion to light due to the increase in pupil diameter), persistence of pharmacologically induced mydriasis (prolongation of the time in which the pupil returns to its original state).

However, keep in mind that, should any disturbance and / or discomfort arise, you will be assisted in the most appropriate way.

BENEFITS

There is no guarantee that you will benefit directly from participating in this study. However, by participating in this study you will contribute to improving the scientific knowledge on the mechanisms that lead to a deficit of visual perception due to the pathology under study (glaucoma).

PARTICIPATION / WITHDRAWAL OF THE SUBJECT

You are totally free to accept or decline to participate in this clinical trial without penalty or loss of benefits and without compromising your relationship with your doctor in any way.

You can withdraw from this clinical trial at any time without prejudice, without having to provide any explanation, without penalty or loss of benefits and without compromising in any way the relationship with the doctor who proposed you to participate in the clinical trial. We only ask you to inform your doctor as soon as possible if you decide to withdraw from the trial.

Your doctor can withdraw you from the clinical trial if this is the best decision in your interest, if the study is suspended or for other reasons. The reasons for the withdrawal will be explained to you.

The interruption of the study may occur by decision of the: Ethics Committee or the investigator.

You will also be promptly informed if information becomes available that may influence your willingness to continue participating in the study.

As a participant in the study, you also have the right to contact the Ethics Committee directly, reporting any discrepancies between the study in which you participate and the information received before giving your consent:

Ethics Committee IRCCS

Session IFO-Bietti

Via Elio Chianesi 53, 00144, Roma

Tel. +39-06-52662719 -2478

If you want, you will also be able to access the documentation relating to the study in question and the opinion expressed in this regard by the Ethics Committee and you will be able to obtain from the doctor any scientific information concerning the study itself.

As part of the study described above, the Promoting Center, in accordance with the responsibilities provided for by the rules of good clinical practice (Legislative Decree 211/2003), will process your personal data, in particular those on health and, only to the extent that they are indispensable in relation to the objective of the study, other data relating to your origin, your lifestyles and other data, exclusively in relation to the implementation of the study in compliance with the provisions of articles 13 and 14 of the General Data Protection Regulation (GDPR) - EU Regulation 2016/679 and the Guidelines for the processing of personal data in the context of clinical trials, Del. 52/08.

The processing of personal data relating to your conditions on the basis of what is required for this study is essential for your participation in the research and for its proper conduct: the refusal to provide them will not allow you to participate in it.

The doctor who will follow you in the study will identify you with a code: the data concerning you collected during the study will be recorded, processed, transmitted to the sponsor and stored together with this code. Only the doctor in charge of the study and the authorized subjects will be able to link this code to your name.

The data, also processed by electronic means, will be collected by the staff of the Center.

Without violating confidentiality, in accordance with the legislation on clinical trials, the staff of the Center / Promoter, the Ethics Committee and the regulatory authorities will be granted direct access to the original medical documentation for the verification of the clinical study procedures and / or data , to the extent permitted by law. Your data will be kept confidential and anonymous to the extent permitted by law and will not be made public. If the results of the clinical trial are published, your identity will remain confidential.

You can exercise the rights referred to in art. 7 of the D.L. 196/03, including the right of withdrawal and rectification of the same data. You will also be able to access all your medical data directly or through a doctor involved in this clinical study, integrate and update them, within the limits set out in the matter of personal data protection. You also have the right to object, for legitimate reasons, to the transmission of data covered by professional secrecy likely to be used in this research.

Any dissemination of the data and the results of the study, even abroad, through scientific publications and / or presentations at congresses, conferences and seminars, will take place in an absolutely anonymous form and therefore your identity will remain confidential.

If you request it, at the end of the study the results of the study in general and in particular those concerning you may be communicated.

You will have the option to terminate your participation in the study at any time and without providing any justification. In this case, no further data concerning you will be collected, without prejudice to the use of any data already collected to determine, without altering them, the search results.

By signing this form, you consent to the processing of your personal data for the purposes of research within the limits and in the manner indicated in the information contained in this document as well as authorizing any access to data concerning you to the representatives of the health and regulatory authorities. as well as authorized personnel.

COMPENSATION

This study will not incur any additional costs for you. At the same time, no compensation is provided for the participants.

We also inform you that you have the right to obtain further information on the trial as it becomes available during the study.

CONCTACT:

Prof. Vincenzo Parisi

IRCCS Fondazione G.B.Bietti – Presidio Britannico, Via di Santo Stefano Rotondo 6, Rome

INFORMED CONSENT

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By signing this form I declare that:

• I have read and understood the Patient Information Sheet (consisting of 8 pages in total) and received clear and comprehensive information.

• I had the opportunity to ask questions to which clear and comprehensive answers were given.

• I understand and I am aware that participation in the research study is absolutely voluntary.

• I give my consent to the use and distribution of my health data as described in the Information Form.

• I have been informed that I can refuse to participate in the study or suspend my participation at any time by communicating this decision to the study doctor; I will not lose any benefits, medical treatment or legal rights that are otherwise due to me.

• I have been informed that I may have to leave the study without my consent if I do not follow the study plan or for some other reason.

• I had enough time to decide whether or not to participate in the trial (since I received a copy of the 8-page information document including this one).

I will receive a signed copy of this consent form.

Name of patient (block letters) _____

Signature_____ Date_____

Name and signature of the legally authorized representative of the patient or of the person giving consent in case of his inability to sign (*if applicable*) _____

Date_____

Name of the doctor who informed the patient (block letters) _____

Signature of the doctor who informed the patient _____

Date_____