PILOT STUDY ABOUT THE EFFECTS OF CALCITRIOL TREATMENT IN NEUROLOGICAL FUNCTION AND FRATAXIN LEVELS PATIENTS WITH FRIEDREICH'S ATAXIA (FA-CALCITRIOL, NCT 480130303)

STUDY PROTOCOL

V1. 29-08-2021

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PACIENT INFORMATION SHEET

PACIENT INFORMATION SHEET AND INFORMED CONSENT FOR PARTICIPATION IN CLINICAL TRIAL:

"Pilot trial about the effects of Calcitriol's treatment in the neurological function and frataxin's level in Friedreich's ataxia patients (FA-Calcitriol)".

Proposed by:

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2. Ataxia Unit. Neurology Department ICS/IAS.

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INVESTIGATORS:

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INFORMATION FOR THE PARTICIPANT

1. GENERAL INFORMATION

We want to inform you about the project **"Pilot trial about the effects of Calcitriol's treatment in the neurological function and frataxin's level in Friedreich's ataxia patients (FA-Calcitriol)",** in which you are invited to participate and that will be carried out by the Spastic paraplegia and Rare diseases Unit of the Neurology Service of the Hospital Universitario Josep Trueta and Hospital Santa Caterina. This clinical trial has been examined and approved by the Ethic and Clinical Investigation Committee (CEIC) of the Hospital Josep Trueta.

The collaboration that we request from you consist in:

- To receive treatment with Calcitriol0.25mcg every day for a year, with periodical neurological, electrocardiographic and blood analysis controls.
- To give 5 blood samples over the year to measure the frataxin's level and various proteins that indicates the antioxidant and mitochondrial function in blood, that will be done in the same periodical blood analysis controls.

To carry out this clinical trial we need your voluntary and free consent. For that reason, we want to provide you with correct and sufficient information in order you can decide about your participation on it. Therefore, we will be grateful if you read this information sheet with attention and you ask us all your doubts.

2. VOLUNTARY PARTICIPATION

You must know that your participation in this clinical trial is voluntary. You may decide not to participate or change your decision and, accordingly, to retire your consent at any moment, without altering the relation with your doctor and without having any prejudice in your treatment. You can request complementary information at any moment.

3. CLINICAL TRIAL DESCRIPTION AND OBJECTIVES

We ask for your participation in the FA-Calcitriol clinical trial because you suffer from Friedreich's ataxia.

The lack of frataxin's protein could be one of the causes of the disease.

It has been observed that:

- The active D vitamin form (calcitriol) can rise the frataxin's production in cells of patients with Friedreich's ataxia.
- The calcitriol synthesis could be impaired in the nervous system of Friedreich's ataxia patients, due the fact that the levels of its precursor (calcidiol) are low in Friedreich's ataxia patients.

Therefore, there is the possibility that the treatment with calcitriol could improve the neurological function in Friedreich's ataxia patients. Nowadays it is not known the appropriate dose. This is the first calcitriol clinical trial and will be carried out with the lowest calcitriol dose (0,25mcg of calcitriol every day) to evaluate if this dose is enough to produce changes in the neurological function and to ensure the drug security and tolerability.

Nowadays doesn't exist any treatment that cures or changes the disease progression.

We propose that the treatment with low calcitriol dose as a potential beneficial treatment to improve the neurological function in Friedreich's ataxia.

The aim of the current clinical trial is to study the calcitriol (the active D vitamin form) effect on:

- The neurological function in Friedreich's ataxia (ataxia, dysarthria, dysmetria).
- The frataxin's blood levels in Friedreich's ataxia patients before and during the calcitriol treatment.

4. PROCEDURES, SAMPLING METHODS AND RISKS ASSOCIATED WITH SAMPLING METHODS.

The procedures that will be carried out during the clinical trial are:

4.1. Blood analysis.

Blood samples will be obtained from blood analysis. Total number of blood analysis: 5

· Initial blood analysis (before staring the treatment).

· Pregnancy test in pre-menopausal women.

· One blood analysis after 15 days under Calcitriol treatment, and at 4th month, 8th month and 12th month under treatment with Calcitriol.

· Measurement the frataxin's level and various proteins that indicates the antioxidant and mitochondrial function in blood, that will be done in the same five blood analysis controls.

The blood sample will be obtained with a normal blood analysis. The associated risks are well known (ex. pain in the puncture zone, haematoma, infection).

The obtained blood samples will be labelled with a code to maintain the confidentiality of the clinical trial's participant.

4.2. Electrocardiogram (ECG).

- Total number of electrocardiograms: 5.

· In the initial visit, after 15 days under Calcitriol treatment, and at 4th month, 8th month and 12th month under treatment with Calcitriol.

The ECG is carried out with an electrocardiogram device, with 10 electrodes in different parts of the body applied with a suction pad or an adhesive.

The risks can be a small irritation and reddening of the zone where the electrodes ara applied.

The objective of the periodic ECG is to rule out any hypercalcemia (rising of blood calcium) complication.

3. Neurological examination.

A medical visit will be performed to assess the neurological function, with various tests and scales (SARA scale and various test: 8-meters-walking test, 9-hole-peg test and PATA test).

It will be performed in the first appointment, and the appointment at 6^{th} month and at 12^{th} month.

5. CLINICAL TRIAL ASSOCIATED RISKS

The associated calcitriol's treatment side effects are scarce. The possible side effects are due the hypercalcemia or rising of calcium blood levels. Calcitriol has been used for decades and its tolerability and security profile is well known. However, as a prudent measure and to decrease the hypercalcemia risk, these patients are excluded from the clinical trial:

- Patients with higher risk of hypercalcemia:

. Cardiac insufficiency or heart failure

. Treatment with certain drugs.

. Long-term immobilisation.

- Patients with hypercalcemia or renal insufficiency.

- Pregnant women.

In case of developing hypercalcemia, symptomatic as well as asymptomatic, these actions will be taken:

1. Withdrawal calcitriol's treatment.
2. Treatment of hypercalcemia.
3. Control blood analysis until hypercalcemia is normalised.
4. Retirement the patient of the clinical trial.

6. BLOOD SAMPLE DESTINATION AFTER THE USE FOR THE CLINICAL TRIAL

Once the clinical trial is finished, the blood sample excess will be destroyed.

7. BENEFITS

In case that Calcitriol is shown to be beneficial for Friedreich ataxia, you will be already taking the drug.

In case that Calcitriol doesn't show any benefit for Friedreich ataxia, probably you won't have any direct benefit from your participation in this clinical trial, but you will have the satisfaction of having collaborated in a clinical trial that can improve the knowledge and the treatment of this disease.

Any discovery that can be implemented on the treatment of the disease will be communicated to you.

You have the right to know the results of the clinical trial. If you decide, you have also the right of not being informed of the results of the clinical trial.

8. RIGHTS AND REGULATORY REQUIREMENTS

8.1. Which data will be collected?

Your medical data will be only collected by the authorized clinical trial researchers and collaborators.

The data that will be collected are data related to:

· Your medical history (age, sex, personal background, the Friedreich ataxia genetic mutations, years of evolution of the ataxia and associated signs and symptoms)

· The clinical scales for the neurological evaluation in the clinical trial (SARA scale, PATA test, 9-hole test, 8-meters-walking test, Barthel's index and life quality questionnaire SF36).

· Blood analysis for calcium's level control and for measurement the frataxin's level and various proteins that indicates the antioxidant and mitochondrial function.

The purpose of the data collection is to conduct Biomedical Research.

The collected data will be analysed with the data of all the participants with the objective to evaluate the efficacy and the security of Calcitriol in Friedreich's ataxia, and to evaluate the effects on frataxin's level.

If the results are positive, this will be communicated in national and international congresses and scientific papers. In every moment, your anonymity and confidentiality will be kept.

The data will not be used for other studies or clinical trials without your previous informed consent.

8.2 How much time will be the data kept?

The data will be saved until the clinical trial objective is reached, and will be eliminated when the legally deadline has expired by the law 14/2007 of the 3rd July of Biomedical Research, with the planned exceptions in the section "rights of the data subjects".

8.3. Who is the responsible of my data?

The data processing, communication and cession of the data subjects will be done with the Regulations (UE) 2016/679 of the European Parliament and the Board of the 27th of April of 2016 of the Data Protection, at it will adjust to the Organic law 3/2018, of the 5th of December, of Personal Data Protection and Digital Rights Guarantee and to the Data Protection of the European Regulations (GDPR, General Data Protection Regulation, approved at 25th of May of 2018).

Your personal data are processed under de Institut d'Assistència Sanitaria (IAS) responsibility, located in the Parc Hospitalari Martí Julià, c/Dr Castany s/n, 17190 Salt

(Girona), electronic mail (*proteccio.dades@ias.cat*) and telephone 972182500. The contact address of the Data Protection Delegate is *dpd@ticsalutsocial.cat*

8.4. How is my confidentiality kept?

The collected data are strictly confidential. To warrant the information confidentiality a coding or pseudonymization: your data and your blood sample will be identified by a code and only the clinical trial doctor and the collaborators would be able to connect your data with your medical history. Hence, your identity will not be revealed to anyone except for a medical emergency, Sanitary Administration request or legal request.

The access to your personal information will be restricted to the clinical trial doctor and the collaborators, sanitary authorities, and the Ethic Research Committee only when is needed to check the clinical trial proceedings and data, but always maintaining the data confidentiality in accordance with the effective legislation.

The data will be collected in the investigation file, which responsability comes from the institution, and will be processed as part of your participation in the clinical trial.

8.5. May my data be shared?

Your data won't be shared to third entities, except in cases specifically planned by law.

However, results and information can be communicated, with previous data pseudonymization, to collaborators only in case they need to be known for the clinical trial research.

In case that your pseudonymized data will be transferred to service centres or other collaborating research groups outside the UE, the data confidentiality will be warranted with specific agreements and contracts and will be for the same clinical trial objectives and used for scientific publications.

Also, all the research results will be anonymous. If personal data publication would be need, we would ask you for personal consent.

8.6. Which rights do I have?

According to the mentioned legislation, you can exercise your rights of:

· Access, rectification, elimination, opposition, and data limitation.

· Transfer of data to a third authorised personal (portability).

· Receive information about your data and the use of it.

· Withdraw your consent. In that case, you must send a written communication and a identity card copy to the contact address above indicated and to the principal investigator of the clinical trial.

To exercise your rights, you should address to the principal investigator of the clinical trial, the doctor Berta Alemany Perna, to the telephone number 972 18 90 44 and/or to the email address *FAcalcitriol@gmail.com*.

Likewise, you have the right to address to the Data Protection Agency if you won't be satisfied. Equally you are informed that you can conduct any query or complaint about data processing to the Administration Data Protection Delegation, to the email address: *dpd@ticsalutsocial.cat.* Also, you can address to the Spanish Data Protection Agency for any complaint about the processing of your personal data.

8.7. Can I decide not to participate in the clinical trial, or can I withdraw from the clinical trial after having given my consent?

Your participation in the clinical trial is utterly voluntarily, and if you decide not to participate you will receive the same medical attention and it won't change your relationship with the medical team.

The clinical trial doctor can retire you from the clinical trial at any moment if exists concern about your health, if you don't follow the clinical trial instructions or if the clinical trial is interrupted. If that happens, the clinical trial doctor will communicate it to you and will ensure that your participation ends properly.

You have the right to retire your consent of participation in the clinical trial at any moment.

If you decide to retire your clinical trial participation consent, any new data will be added to the database. If you stop participating, we remember you that the prior collected clinical trial data can't be eliminated to warrant the research validity and to obey with legal duties and drug authorization requirements.

8.8. Can my data be used in other clinical trials?

Likewise, you give your consent that the clinical trial data can be used, with the same pseudonymisation guarantees, for other clinical trials and investigations that can be conducted by the present clinical trial responsible. In that case you will be previously informed of the new clinical trial/investigation purpose.

9. ECONOMIC COMPENSATION

The clinical trial participation and the donation of biological human simples are for free. Therefore, your participation in the clinical trial will not receive any economic compensation.

In the event that a commercial development from the generated knowledge occurred, the possible profits would go entirely to support the scientific objectives of the research group. By signing this consent, you renounce to any right of commercial use of the information and samples that you are giving.

INFORMED CONSENT OF THE PILOT CLINICAL TRIAL ABOUT THE EFFECTS OF CALCITRIOL'S TREATMENT IN THE NEUROLOGICAL FUNCTION AND FRATAXIN'S LEVEL IN FRIEDREICH'S ATAXIA PATIENTS (FA-CALCITRIOL)

I, Mr./Mss. ....., with Identity Card number, ...resident in .....

Dr. Berta Alemany has proposed me to participate in **"Pilot clinical trial about the effects of Calcitriol's treatment in the neurological function and frataxin's level in Friedreich's ataxia patients"**.

- I have read the information sheet.
- I have received enough information about the clinical trial.
- I have had the possibility of asking questions.
- I understand that my participation is voluntary. I can change my opinion and/or I can withdraw from the clinical trial at any moment, without that my medical assistance or my legal rights can be affected.
- I understand that I have the right of access, rectification, elimination, opposition, and data limitation, even of transfer of data to a third authorised personal (portability), according to the Organic law 3/2018, of the 5th of December of Personal Data Protection and Digital Rights Guarantee.
- In the event that the investigations results provide data that could be interesting for me or for my relatives (please fill in one of the boxes):

□ I want to be informed to the telephone number..... or email .....

□ I don't want to be informed.

- I understand that the obtained biological simples will be labelled with a code to maintain my data confidentiality and that, according to the law 14/2007 of the 3rd July of Biomedical Research, the excess sample will be destroyed.
- I understand that I can revoke my consent at any moment, without explanation and without being affected my medical assistance.

If I need more information about this clinical trial I can contact with the principal investigator, Dr. Berta Alemany Perna, at the telephone number 972 18 90 44 and/or at the email *FAcalcitriol@gmail.com*.

To clarify my decision, I have received and understood the following information:

1.The research is destined to prove the calcitriol's effects in Friedreich ataxia patients and in the frataxin's levels.

2. My participation consists in taking calcitriol and in blood samples collection to measure the frataxin's level and various proteins that indicates the antioxidant and mitochondrial function in blood, and to control the blood calcium's levels.

The associated risks are those due the blood analysis and the possible calcitriol's side effects, of which I have been properly informed.

I authorise to be contacted in case of the need for more information or additional biological samples: **YES** ☐ **NO** ☐

Telephone: ..... Email: .....

I ACCEPT TO PARTICIPATE IN THIS CLINICAL TRIAL WITH THE AFOREMENTIONED CONDITIONS

I freely give my approval to participate in the clinical trial and I give my consent to the access and using of my data in the aforementioned detailed conditions:

In Salt (Girona), on ……..of ....., ...

Researcher's signature

Dra. Berta Alemany Perna

Participant's signature

Name:.....

Identity number:.....

Patient's legal representative signature

Name:.....

Identity number: .....