INFORMATION LETTER AND CONSENT FORM for PARENTS

Clinical trial

University Hospital Centre of Orléans

Effect of nutritional management of children with sickle cell disease on bone mineral density and body composition

Sir, Madam,

Your child has sickle cell disease, the most common hereditary disease of the red blood cell. Your child's symptoms are linked to hemolysis (rupture of red blood cells) and vaso-occlusion (obstruction of blood vessels). As your doctor has informed you, your child may present with acute painful crises called vasoocclusive crises (VOC), chronic pain, acute and chronic anemia, infections and damage to several organs. It is also shown that osteoporosis (bone transparency) is much more common. A child with sickle cell disease expends more energy, even when resting, compared to a healthy child.

During these complications your child may eat insufficiently.

In the current state of knowledge, doctors do not have reliable recommendations regarding the proper nutrition of children with sickle cell disease.

In these circumstances, we would like to involve your child in a therapeutic nutritional trial.

Before agreeing to participate in this research project, please take the time to read and understand the information that follows. This document explains the purpose of this research project, its procedures, advantages, risks and disadvantages. We invite you

to ask any questions you deem useful to the person presenting this document to you. You can refuse to participate in this study at any time without prejudice.

Purpose of the study:

The main objective of this therapeutic trial will be to check whether an increase in nutritional intake will improve your child's bone mineral density (bone strength) and body composition (muscles).

Our secondary objectives are to verify whether this increase in nutritional intake can be beneficial for growth, complications of sickle cell disease (VOC, chronic pain, acute and chronic anemia, infections), school absenteeism, cardiac function, cerebral vasculopathy and biological parameters for monitoring your child. We also wish to keep blood samples from your child in order to carry out later during a future study dosage of different substances (cytokines of inflammation, markers of oxidative stress and other bio-markers according to updated data from the literature) for the purpose of scientific research to better understand the effect of nutrition on sickle cell disease.

How is this going to happen?

In addition to the usual care and monitoring, if you accept that your child participates in the study, we will draw lots to find out whether your child enters the *"nutritional supplement" group* or the *"control" group*. If your child falls into the "nutritional supplement" group, he will receive an oral nutritional supplement increasing his caloric intakes by approximately 20%. He/she will therefore have to consume once or twice a day a high-calorie and balanced nutritional product, of liquid consistency, in quantities of 200 to 400 ml per day for 1 year.

If your child enters the control group, he/she will keep his usual nutritional intake and will not have to change his eating habits.

Whether your child is in one or other of the groups, the following will be carried out:

* Measurements by dual-photon absorptiometry of your child's bone mineral density (bone strength) and body composition (muscles) will be taken 2 times: at inclusion, and 12 months late. This device allows you to measure bone mineral content (BMC), BMD and body composition PAINLESSLY and in 3 minutes. This examination is safe since it delivers irradiation TEN TIMES LOWER THAN THAT OF A PULMONARY X-ray. Thus, the densitometric measurement exposes a maximum to irradiation of 1.92µSv to 6.77µSv.

For comparison, a pelvic scanner exposes at 6000 µSv, a lateral incidence x-ray of the lumbar spine at 530 µSv, and a mammogram at 450 µSv.

These are therefore rates much lower than the annual natural irradiation that we receive in France which is 2 mSv, knowing that we must add 1mSv for every 3000m of altitude. During air transport, average exposure is 2 to 4 µSv per hour.

Additionally, there is no evidence of effects on human health below 100 mSv.

* quarterly nutritional monitoring: a dietitian will ask you to specify what your child eats. Depending on your answer, with the doctor's agreement, she will prescribe the oral nutritional supplement (if your child is in the "nutritional supplement" group) that your child will have to drink. She/He will ask you to keep the empty packaging and return it to her. You will also need to keep a food tracking diary to note how much product your child drinks every day. You will see the dietician at the same time as you meet your hospital doctor. You will therefore not have to come back more often than usual, i.e. every 3 months. She/He will telephone you 6 weeks after each consultation to check if your child has difficulty consuming this product.

* In addition, if you agree, we would like to keep samples of 10 ml of your child's blood: on 2 occasions, one at inclusion, and one 12 months later. We wish to

carry out later during a future study dosage of different substances (cytokines of inflammation, markers of oxidative stress and other bio-markers according to updated data from the literature) for the purpose of scientific research to better understand the the effect of nutrition on sickle cell disease. These samples will be frozen and stored at -80°C in the Biopathologies Unit of The University Centre Hospital of Orléans.

* The data collected during traditional monitoring of your child's pathology will also be used (medical examinations, imaging, questionnaires, etc.), in an anonymized manner, as part of this research. They can also be used when analyzing the serum library, always in an anonymous manner.

If your child ever becomes overweight during follow-up, we will immediately stop consumption of the Oral Nutritional Supplement. We will set up prolonged medical monitoring by a specialist and dietician with a view to a normal-calorie diet and appropriate physical activity, until your child returns to a normal weight.

If your child receives the oral nutritional supplement, you will need to bring back the empty packaging at each visit, which will allow us to ensure proper consumption of the product.

In addition, you and your child should answer a school absenteeism questionnaire at baseline, then every 3 months.

The planned duration of the study is 1 year, but you will not have to return to the University Hospital Centre of Orléans more frequently than as part of your usual follow-up.

What are the expected benefits?

This study allows your child to benefit from prolonged nutritional monitoring. Likewise, benefits in terms of public health are expected such as improvement in bone strength

and body composition (musculature). Complications of sickle cell disease may be less common and/or less severe if your child's nutritional status is better. All this would allow the optimization of the care of children with sickle cell disease.

What are the risks and constraints?

These examinations are painless, non-invasive and have a low irradiation rate, much lower than those of a traditional x-ray. The dose is 1/10th of that received by a patient undergoing a chest x-ray.

3. Participation in other studies:

The research protocol does not provide for a ban on participating simultaneously in another research study, nor for an exclusion period during which participation in another research study is prohibited.

What are your rights?

Your child's doctor must provide you with all the necessary explanations concerning this research, the purpose of which meets the criteria of public interest. If you wish to remove your child at any time, and whatever the reason, he/she will continue to benefit from medical monitoring and this will in no way affect his/her future monitoring.

As part of this research, computer processing of your child's personal data will be implemented to enable the results of the research to be analyzed with regard to the objective of the latter which has been presented to you.

This processing complies with the regulatory provisions allowing a health establishment to process data for scientific research purposes. The person responsible for this processing is the University Hospital Centre of Orléans, promoter of the research. In accordance with the European Data Protection Regulation, the University

Hospital Centre of Orléans has appointed a data protection delegate who you can contact at the following email address: dpo@chr-orleans.fr.

To this end, medical data concerning your child will be transmitted to the research promoter or to the people or companies acting on his behalf, in France or abroad. This data will be identified by a code and/or your initials. These data may also, under conditions ensuring their confidentiality, be transmitted to French or foreign health authorities and to other entities of the University Hospital Centre of Orléans.

The University Hospital Centre of Orléans, as part of future collaborations, may also transfer this coded data to institutional or industrial scientific teams in France or around the world in order to continue research on the subject or for scientific research purposes in accordance with General Data Protection Regulation (GDPR).

Furthermore, in accordance with the provisions of the law relating to data processing, files and freedoms (law of January 6, 1978 as amended), and European Regulation 2016/679 of April 27, 2016 (GDPR), you have at any time 'a right of access, rectification, portability and limitation of your child's personal data. You can also lodge a complaint with a supervisory authority (CNIL for France). You also have the right to object to the transmission of data covered by professional secrecy that may be used in the context of this research. and to be processed. Exercising this right involves withdrawing your consent to participate in the trial. In this case, the data obtained before it was removed will be used in the research.

During or at the end of the research, you can access directly or through the doctor of your choice to all of your child's medical data in accordance with the provisions of article L1111-7 of the code of public health and the GDPR of the European Union n°2016/679. These rights are exercised with the doctor who follows your child as part

of the research and who knows his or her identity or the Data Protection Officer of the University Hospital Centre of Orléans.

Your child's data will be retained throughout the research. After the end of the research, the data will be archived for a period in accordance with regulatory provisions (minimum 15 years), then destroyed.

In accordance with the public health code and decree n°2017-884 of May 9, 2017,

o this research obtained a favorable opinion from the Committee for the Protection of People (French ethics committee)

o The National Agency for the Safety of Medicines and Health Products (ANSM) has been informed of this study.

o when this research is completed, you will be kept personally informed of the overall results by your doctor as soon as they become available, if you wish.

After reading this information note, do not hesitate to ask your child's doctor any questions you have. After a period of reflection, if you agree to participate in this research, you must sign your consent to participate in this study. A copy of the complete document will be given to you.

CONSENT

(3 copies: 1 for the father, 1 for the mother, 1 for the investigator)

Child’s first and last name……

Mother of the child (or legal representative)

I, the undersigned (last name, first name):

consent:

□ for my child to participate in the research entitled: “Effect of nutritional management of children with sickle cell disease on bone mineral density and body composition”

□ for my child to take part in creation of blood-bank

I have read the form and understood the purpose, nature, advantages, risks and disadvantages of the research project. I am satisfied with the explanations, details and answers that the researcher provided me, where applicable, regarding my child's participation in this project.

Date and signature of the mother:

Father of the child (or legal representative):

I the undersigned (last name, first name)

consent:

□ for my child to participate in the research entitled: “Benefit of nutritional management of children with sickle cell disease on bone mineral density and body composition

□ for my child to take part in creation of blood-bank

I have read the form and understood the purpose, nature, advantages, risks and disadvantages of the research project. I am satisfied with the explanations, details and answers that the researcher provided me, where applicable, regarding my child's participation in this project.

Date and signature of father:

Date and signature of the investigator:

INFORMATION LETTER AND CONSENT FORM (Children aged 12 to 16 years)

Clinical trial

Effect of nutritional management of children with sickle cell disease on bone mineral density and body composition

Your parents have accepted that you participate in the trial proposed by our doctors in the University Hospital Centre of ORLEANS. This research will be carried out in association with our dietitians.

Take the time to read and understand the information that follows to find out if you too agree to participate.

This document explains the purpose of this research project, its procedures, advantages, risks and disadvantages. We invite you to ask all the necessary questions.

Nature of the study:

The aim of this study will be to check if a good diet can improve your bone strength and musculature (body composition). We also want to see if the problems linked to your illness – pain, fever, fatigue, shortness of breath, school absences – would be less frequent if your diet was higher in calories.

With your agreement, we will keep samples of your blood taken during the usual check-ups for future scientific analyses.

Procedure for participation:

During this study you may be eligible to receive a food supplement (“fortifying milk”), through a random drawing system.

Our dietitians will follow you closely, as will our doctors.

We will keep samples of your blood 2 times - at baseline, and 12 months later in order to analyze your inflammation later.

If you are overweight during follow-up, you will be excluded from the study.

If you receive the oral nutritional supplement, you should not throw it away once drunk, because we want to collect the empty packaging to let us know that you are drinking the product.

The expected duration of the study is 1 year.

Possible benefits, risks or disadvantages related to your participation:

During this study you will benefit from the usual monitoring by your doctor.

In addition, a dietitian will monitor your nutritional status.

Examining your bone density and body composition is not dangerous for your health even if it is carried out twice in 1 year. We will try to do it one day when you consult your hospital doctor.

The samples of your blood taken twice in 1 year will correspond to blood tests that your doctor must carry out anyway. The amount of blood drawn will be small so that you will not be tired.

The benefits of this study are linked to the results (of these examinations and your usual follow-up) which will allow us to know if increasing your diet can improve your bone condition, your musculature, but also the complications of your disease and therefore, your health.

All your personal data will be used anonymously for research.

We thank you for taking the time to read this newsletter. Your collaboration is valuable for carrying out the research.

INFORMATION LETTER AND CONSENT FORM (Children aged 6 to 11 years)

Clinical trial

Effect of nutritional management of children with sickle cell disease on bone mineral density and body composition

Your parents have given us permission for you to participate in research concerning your disease.

We, your doctors, want to know if when you eat better you will feel better.

Do you also agree to participate?

You will regularly see our dietitians who will talk to you about your diet.

The goal of this study is to show a relationship between your diet and the strength of your bones, your muscles, and the problems related to your illness – pain, fatigue, fever, absences from school.

Your participation consists of

- Follow the dietary advice, and eat, if they ask you, a “fortifying milk”

- Allow us to measure the strength of your bones and muscles (by taking a sort of photo using the device below).

- Allow us to preserve and analyze your blood by scientists

All this information, and that concerning you for monitoring your disease, will then be used for the study, without ever naming you.

Your results will remain a secret.

Do you have questions?

Thank you for your participation.