

**CLINICAL TRIAL OF BIOMEDICAL RESEARCH  
Information Form for Patients  
Participating in this Research**

**Sponsor and Investigator: Dr. Michel Assor  
Knee and Lower Limb Institute, Marseille, France  
Vert Coteau Clinic, 96 Avenue Caillols, 13012 Marseille  
www.cellulesouches.org**

**Title of clinical trial:**

**Using Mesenchymal Stem Cells Autologous Bone Marrow Stimulated by  
demineralized bone matrix on Absorbable Scaffold to heal Articular Cartilage  
Defect and Osteoarthritis Knee**

**Authorization of the competent authority, French Health Agency AFSSAPS  
16/02/2010, Ref : B91251-10  
Authorization Committee of Protection of the Person  
Southeast IV June 8, 2010, Ref : 10/033**

Madam, Sir,

We invite you to participate in biomedical research or clinical study. Before you decide, it is important that you understand why this study is, what the study entails, the benefits, risks and potential drawbacks.

Take your time to read this information note intended to answer any questions you may have about this study, and if you want, talk with your family, your friends or your referral doctor. You can also contact your physician-investigator who proposed the study and ask any questions you want.

**1. WHAT IS THE PURPOSE OF THE STUDY?**

You are between 30 and 70 years and are suffering from osteoarthritis of the knee chondral defect size or limited: area without cartilage with exposure of bone (injury grade III to IV), smaller than 6 cm<sup>2</sup> and located at internal condyle (and / or tibia in some cases), and whose origin is variable (trauma, sports, osteoarthritis, osteonecrosis, osteochondritis dissecans).

It is necessary to participate in this study: (1) that the knee is stable anterior cruciate ligament present or reconstructed , (2) 3 / 4 of the meniscus is present, or meniscal transplantation performed, (3) The knee is not misaligned with one axis less than 5°, or osteotomy advance.

The chondral defect is the starting point of cartilage degeneration and osteoarthritis advanced, there is no spontaneous evolution towards clinical improvement : the cartilage can not regenerate itself.

Current techniques for repair or restoration of areas articular cartilage have unpredictable results and high rates of failure.

The aim of the study is: (a) to regenerate cartilage naturally (or hyaline cartilage), using your own stem cells (mesenchymal) in bone marrow aspirates (in the pelvis: iliac crest), activated with demineralized bone and implanted directly – without culture expanding, in one step- on the knee, against the area with exposed bone, under arthroscopy, (2) to restore normal hyaline cartilage filling the defect of the knee cartilage, and to avoid osteoarthritic degradation, thereby preventing the progressive deterioration of cartilage degeneration, (3) and evaluate the progress of the results by comparing clinical scores and imagery (x-rays and MRI) before and after surgery.

The technique proposed here is new, without culture, tested on animals, natural regenerating hyaline cartilage with consistent results, and that experimentation (or application) begins in humans.

The technique of using mesenchymal stem cells is very recent, used by some teams, with or without culture in various orthopedic disorders, with inconsistent results. But no use stem cells stimulated by demineralized bone matrix, which contains proteins that cause growth of these stem cells into bone or cartilage, as proposed in this clinical trial.

## **2. WHAT IS THE COURSE OF THE STUDY? WHAT WILL THE TREATMENT? WHAT ARE THE TESTS TO BE CARRIED OUT?**

### **β In practice:**

After reading this document and if you agree to participate in this study, your doctor will ask you to sign a consent form to participate.

Before starting treatment, initial medical evaluation will be conducted to determine whether you meet all the criteria required to participate in this study.

The medical evaluation will include the following tests: preoperative assessment classical blood test, cardiopulmonary assessment, and examination of the knee by the surgeon :calculation of clinical scores, radiographs, measurement of axis knee, and MRI (or any CT scan).

These reviews are part of the usual care and will be made anyway if you do not participate in this study. Fees will be required.

### **β Treatment:**

Step 1: selection of patients, according to the restrictive framework of the clinical trial

2nd stage: in the operating room, the autologous bone marrow cells are removed by suction to the syringe on the iliac crest;

3rd stage: the stem cells are isolated and concentrated using a centrifuge, still in the operating room;

4th stage: arthroscopic knee osteoarthritic lesion preparation and debridement of any other lesions;

5th stage: the preparation containing stem cells (and Platelet Rich Plasma PRP) is mixed with demineralized bone matrix, and collagene-calcium hydroxyapatite (Collapat), which sets the stem cells, and appears as a semi-malleable;

6th step: implantation of stem cells in the damaged area under joint arthroscopy, completely covering it and fixing it with absorbable mesh son. Then injection of PRP.

7th step: The patients will be assessed according to the timetable for monitoring, evaluating clinically and with imaging studies (MRI and radio) of the reconstruction of cartilage.

### **β Your follow:**

Three visits, with routine clinical examination of knee and general condition will be made at 2nd and 4th week, and between the 6th and 8th week, in order to verify progress and post-operative scarring knee, and the absence or presence of incidents or postoperative complications.

Three visits will be conducted on the 3rd, 6th and 12th month, with calculation of two clinical scores.

Knee radiographs are made during these three periods, and MRI (or if the CT scan) is performed in the 6th and 12th months.

A biological assessment with blood inflammatory balance is sought on the 2nd month.

### **3. WHAT BENEFITS TO WAIT OF MY PARTICIPATION IN THIS STUDY?**

The expected benefits for patients participating in clinical trials, bearing a degenerative knee in the femoral condyle (grade IV cartilage defect type 6 cm<sup>2</sup> maximum with possible lesion associated in tibial grade II to III) is stop the degradation and degeneration of cartilage, reconstruction and re-growth of hyaline cartilage filling the area osteoarthritic, improve joint function and reducing the pain syndrome.

### **4. WHAT ARE THE RISKS ANTICIPATED?**

No specific risks associated with the use of these stem cells in one step and without culture, were identified : no infection, no excessive formation of new bone, no induction of tumor formation, no morbidity due to aspiration of bone marrow from the iliac crest. The absence of culture avoids manipulation.

The inherent risks are mechanical : the lack of integration of the composite cell against cartilage defect and the absence of articular cartilage layer formation and the detachment of the composite cell in the joint (spontaneous degradation); worsening degeneration and osteoarthritis functional disability that may require further surgery.

Risks related to arthroscopic surgery: stiffness, phlebitis, hematoma, effusion, sepsis, which may require special treatment.

## **5. WHAT ARE THE LIMITATIONS RELATED TO THE STUDY?**

The duration of patient participation in clinical trials is 1 year, with the inspections, the realization of radiographs at 3, 6 and 12 months postoperatively, and MRI at 6 and 12 months.

Postoperatively, the full mobility of the knee is allowed, walking is permitted, protected by a pair of crutches with partial weight bearing for 3 weeks, and rehabilitation of 2 to 3 months.

The medical management with current treatments is provided in case of further degenerative joint disease, end of the search or after premature discontinuation of treatment or exclusion from the research.

## **6. WHAT HAPPENS THERE IF I REFUSE TO PARTICIPATE IN THIS STUDY?**

Other traditional methods of cartilage repair will be offered, such as micro-fractures, abrasion arthroplasty, arthroscopic most often to fill the cartilage defects, which improved in 70% of cases, and on surface defects reduced. But so far none has been able to produce normal hyaline cartilage, but a fibro-cartilage, with progressive deterioration over time.

Other restoration techniques (grafting osteochondrale autologous transplantation of autologous chondrocytes), have their own limitations prevented wide clinical use. Total Knee Arthroplasty (TKA) is a good solution is the destruction of your cartilage is too advanced.

## **7. YOUR RIGHTS**

### **β Your participation in this research is entirely free and voluntary**

You are free to accept or refuse to participate in the study that is offered. If accepted, you are free to change during the study and stop your participation at any time. Your acceptance or refusal will not affect the relationship you have with your doctor will continue to offer care that he considers most suitable to your health.

### **β Your doctor and the promoter of this study have the potential to interrupt if necessary**

Similarly, your doctor is able to stop treatment if it is deemed in your best interest: for example in case of progression of your disease, in cases of poor tolerance, if the study is interrupted or if you can not follow its rules.

The promoter of this study which provides management and accountability is Dr. Michel Assor. He may decide to stop the study.

### **β Your information is strictly confidential and anonymous**

Your medical records remain confidential and can not be viewed as the responsibility of the physician in charge of your care and by health authorities and by persons duly authorized by the trial sponsor and subject to professional secrecy.

To enable the analysis of research results, computer processing of data recorded during this study will be implemented. In accordance with the Law on Informatics and Freedoms (Act No. 78-17 of 6 January 1978 amended) you have a right to access, rectify and object to your data. This right is exercised with your doctor who only knows your identity.

**β A responsibility insurance covering the study was underwritten**

Under French law, the Promoter has taken out a policy of liability insurance covering the conduct of this study, at the company Gerling France, 111/113 rue de Longchamp, 75116 Paris, Police No. 200900199.

**β The study is conducted in accordance with the Code of Public Health for biomedical research**

In this context, the Competent Authority (French Agency of Health Products - AFSSAPS) has approved this trial on 16/02/2010, under reference: B91251-10.

In addition, it received the favorable opinion of the Committee of Protection of the Persons South East IV dated 06.08.2010, under N° 10/033.

**β You will be informed of the results of research**

In addition, under the Act No. 2002-303 of 4 March 2002, you will be told by your doctor, upon request, the overall results of the study once it is completed.

**8. IF YOU WANT MORE INFORMATION**

Your doctor, Dr. Michel Assor, phone: 0033491221212 / 0033491186544 remain responsible for your treatment.

He is the person to contact if you want more information about this study or any other element.

If you agree to participate in this study, we ask that you give your written consent by signing and dating the attached form. This signature does not release the physician's responsibility and it just confirms that you have been informed of this study and that you participate freely.

Date: ... .. / ... .. / ... ..

Signature Patient

Signature Investigator  
Dr Michel Assor

**CLINICAL TRIAL OF BIOMEDICAL RESEARCH  
Participation Consent Form  
a Biomedical Research**

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16/02/2010, Ref: B91251-10**

**Authorization Committee of Protection of the Persons:  
CPP southeast IV June 8, 2010, Ref. : 10/033**

I, undersigned,

Mrs., Ms., Dr.

.....  
Born .....  
Address .....  
.....

Says:

- That Dr. Michel Assor, Orthopaedic Surgeon, asked me to participate in the study named above,
- He told me in detail the protocol,
- It makes me particularly aware of:
  - the purpose, method and duration of the study
  - constraints and risks involved (list below)
  - any other treatment options
  - My right to refuse to participate in the event of disagreement and to withdraw my consent at any time
  - my registration requirement for a social security scheme
  - that, if I want to close, I'd be informed by the medical investigator's overall results
  - AFSSAPS that has issued an authorization on 12/02/2010 for this study: Ref. Afssaps: B91251-10
  - The Committee of Protection of the Persons South East IV issued a favorable opinion dated June 8, 2010, Ref. : 10/033
  - that in the context of the study sponsor, Dr. Michel Assor, has taken out insurance (company Gerling France) for this research.
- I responded in good faith to questions about my health and my participation in other studies (excluding other studies for 1 year).

- Summary of potential risks:

degenerative changes with continued deterioration of the cartilage of the knee, despite the attempt of cartilage repair. It has not been found in the literature of specific complications related to use of mesenchymal stem cells (no infection, no of excessive formation of new bone, no induction of tumor formation, no morbidity due to bone marrow aspiration from the iliac crest). Specific risks are mechanical: the lack of integration of the cell composite against the cartilage defect and the absence of articular cartilage layer formation, and the detachment of the composite cell in the joint (spontaneous degradation) ; further worsening osteoarthritic degeneration and functional impairment that may require reoperation. The risks of arthroscopic surgery: stiffness, phlebitis, hematoma, effusion, sepsis.

I received this doctor a clear and accurate information regarding the natural history of disorders or disease which I suffer if I did would not operate.

I was informed that any surgery has a rate of complications and risks, including vital, taking not only the pathology of which I am assigned, but also to individual variations not always predictable. I have also been informed that during the intervention, the practitioner may be faced with a discovery or an unexpected event requiring additional procedures or different from those initially planned. All these information was given orally and a written document, which I read, was given to me. I recognize that the nature of the intervention and its advantages and risks were explained to me in terms I understood and that I have been satisfactorily answered all the questions I asked.

The information collected in the study by the investigator are treated confidentially.

I agree:

- The data recorded during this research can be computer processed anonymously. I understand that the right of access under the Act of 6 August 2004 relating to data, files and freedoms exercised at any time with the doctor who follows me through the research and knows my identity. I may exercise my right to rectification and opposition with this same doctor, who will contact the sponsor of research.

**After talking freely and answering all my questions, freely and voluntarily agree to participate in the biomedical research under the conditions specified in the form of informed consent.**

Name and surname of the patient:  
.....

Date: ... .. / ... .. / ... ..

Signature

Preceded by the words "Read and understood"

Name of investigator:  
... .. Michel ASSOR, MD... ..

Date: ... .. / ... .. / ... ..

Signature

This document is to be realized in two copies, the first of which must be kept for 15 years by the investigator, another given to the person giving consent.