A Clinical Study to Evaluate the Safety and Effectiveness of NOVOCART® 3D plus Compared to Microfracture in the Treatment of Articular Cartilage Defects of the Knee

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Primary ObjectiveTo demonstrate that the effectiveness of the NOVOCART® 3D plus autologouschondrocyte transplantation system is superior to microfracture for the treatment ofarticular cartilage defects of the knee by demonstrating superiority of the...

Ethical review	Not approved
Status	Will not start
Health condition type	Tendon, ligament and cartilage disorders
Study type	Interventional

Summary

ID

NL-OMON40824

Source
ToetsingOnline

Brief title
NOVOCART® 3D plus (N3D) Study

Condition

- Tendon, ligament and cartilage disorders
- Bone and joint therapeutic procedures

Synonym
cartilage defects - cartilage damage

Research involving
Human

Sponsors and support

Primary sponsor: TETEC AG
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Articular cartilage defects, knee, Microfracture, NOVOCART® 3D plus

Outcome measures

Primary outcome

The primary endpoint is the patient*s functional outcome as measured by the change in the 2000 IKDC subjective knee form scores from baseline to the 36-month followup assessment.

Secondary outcome

* Change from baseline to 36-month visit in the Knee Injury and Osteoarthritis Outcome Score (KOOS).

* In vivo performance measured by the 36-month assessment of the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score. These assessments will be performed on a subset of patients (64 in each group) as described in the attached radiological study protocol

* Change from baseline to the 36-month visit in the IKDC objective physician score.

* Change from baseline to the 36-month visit in the SF-36 to measure clinical utility and summarize health-related quality-of-life and cost-effectiveness.

* Change from baseline to the 24-month visit in the above patient-reported

outcomes.

* Surgical time (cut-to-suture time).

* Length of incision.

Study description

Background summary

Articular cartilage injuries of the knee can lead to premature wear of the joint and subsequent arthrosis. Conservative treatments merely treat the symptoms of the disease and do not bring about any fundamental healing of the lesions. If symptoms (e.g., pain) become more problematic, surgery is typically recommended. There are several reparative surgical techniques used to treat chondral cartilage defects of the knee. Reparative techniques include microfracture, allograft reconstruction, autologous osteochondral transplantation (*OATS** or *Mosaicplasty**) and autologous chondrocyte transplantation or implantation (*ACT* or *ACI*). Bone marrow-stimulating procedures such as microfracture mainly result in replacement tissue that is inferior to natural hyaline cartilage in biomechanical properties and viscoelastic characteristics. Osteochondral transfer procedures provide hyaline cartilage to the grafted site, but there is a risk of donor site morbidity, limiting these procedures to small defects. ACT is a treatment option that differs from other reparative techniques in that it allows formation of hyaline-like repair tissue. Five year results have recently become available from a prospective, randomized study on conventional ACT using chondrocytes versus microfracture in patients with clinical symptoms of not more than three years. Clinically, ACT proved to be significantly better than microfracture, and the difference was therapeutically relevant.
TETEC has developed NOVOCART® 3D plus Autologous Chondrocyte Transplantation System, a cell-scaffold combination product composed of ex vivo expanded autologous chondrocytes seeded on a bioresorbable biphasic collagen scaffold transplanted using a minimally invasive approach. NOVOCART® 3D plus was developed to facilitate healing with normal replacement cartilage with the application of chondrocytes in a robust three-dimensional scaffold transplanted using a minimally invasive procedure.
A retrospective survey of NOVOCART® 3D plus was conducted in Europe with a total of 422 patients. The purpose of the survey was to gather information on adverse outcomes, and changes from baseline in measures of pain, function, and swelling. Review of the retrospective survey results shows an acceptable safety profile combined with significant improvements in pain, function and swelling. Based on the satisfactory results of the retrospective survey, TETEC AG is conducting this clinical study.

Additional clinical evidence of the effectiveness of NOVOCART® 3D plus will be obtained by conducting this large, long-term, randomized, controlled clinical study. Patients will be randomized to one of the two study arms to protect against potential selection bias. The control therapy, microfracture, is a proven therapy considered to be the current standard of care. The clinical study design calls for an interim analysis that allows the efficient use of data to reach an early conclusion of the study without sacrificing scientific rigor, thereby minimizing burden on the participating patients and investigators.

Study objective

Primary Objective
To demonstrate that the effectiveness of the NOVOCART® 3D plus autologous chondrocyte transplantation system is superior to microfracture for the treatment of
articular cartilage defects of the knee by demonstrating superiority of the subjective
IKDC score improvement from baseline to the score measured at the 36-month assessment visit.
Secondary Objectives
* To assess the physician evaluation of the functional effectiveness of NOVOCART® 3D plus.
* To evaluate health-related quality-of-life improvement.
* To evaluate cartilage (tissue-structure) regenerative effects of NOVOCART® 3D plus.
* To assess surgical parameters.
Safety Objective
The safety objective of the study is to demonstrate the safety of the NOVOCART® 3D
plus autologous chondrocyte transplantation system when used as intended. The safety results of NOVOCART® 3D plus will not be compared to microfracture because of the distinctive risk profile and safety expectation for NOVOCART® 3D plus.

Study design

This is a prospective, randomized, multi-center, unmasked clinical study designed to
demonstrate the superiority of NOVOCART® 3D plus compared to microfracture for the treatment of articular cartilage defects of the knee. The study requires a 36-month follow-up period for the pivotal phase to achieve its primary and secondary
objectives. Study participants will be followed in a 5 year (post surgery) long-term
follow up phase to collect long-term data. The arthroscopic microfracture

technique of
Steadman will be used in conjunction with a defined rehabilitation program. The study uses a sequential design to compare NOVOCART® 3D plus to microfracture procedure on patients. The design of the study allows one pre-planned interim analysis using the data from the first 67% patients who complete their 36-month follow-up to assess the primary endpoint. If the evidence is found to be significant,
against the O*Brien-Fleming boundary and in favor of NOVOCART® 3D plus, an early claim of study success will be made. The study will be continued until the enrollment
ceiling has been reached and all participating patients have completed the study. A
final report including all enrolled patients will be submitted to update the European
Public Assessment Report (EPAR) and product labeling.

Intervention

* TETEC AG NOVOCART® 3D plus Autologous Chondrocyte Transplantation System.
OR
* Microfracture technique according to Steadman._

Study burden and risks

Benefits.
Based on current knowledge about the mechanism of action of the ATIMPs and the promising results from animal studies and from human therapeutic experience with the product NOVOCART® 3D plus and similar therapeutic principles,
it is expected that the patients who participate in this clinical study will benefit from
the treatment with the ATIMP. Signs and symptoms of the underlying disease are anticipated to improve such that oral pain therapy can be reduced or even tapered
off.
Scientific Benefit.
Laboratory studies and earlier surveys in humans using similar approaches for traumatic diseases of the knee have already suggested that the ATIMP can significantly improve the outcome of such patients. Hence, this clinical
study will serve to scientifically evaluate the response of patients suffering from
trauma associated changes in the knee. If the results are positive, further investigations will be conducted in order to expand the indication for all patients with
trauma-associated cartilage defects.

It is necessary to develop and evaluate new, promising and easy-to-handle therapeutic alternatives for trauma-associated cartilage defects, considering increasing numbers of patients and the lack of alternatives to prevent secondary degeneration in patients suffering from this disorder.

Risk-Benefit Assessment.
The currently known risks of adverse reactions to the
ATIMP, or those associated with the medical procedures that are used during the study in order to handle the ATIMP, are very small when considering the expected improvement to the individual participant or to the entire group of patients suffering
from this disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

*Patient is * 18 and * 65 year old at time of screening
*Patient has a localized articular cartilage defect of the femoral condyle or the trochlea of the knee. 2 localized cartilage defects are accepted if the total defect size is * 6 cm2 post-debridement, both cartilage defects are located at the femoral condyle and/or the trochlea and both cartilage defects are to be treated with NOVOCART® 3D plus or microfracture..
* Patient has a defect size * 2 and * 6 cm2post-debridement.
* Patient has an intact (< Grade 2 ICRS classification) articulating joint surface (no *kissing lesions*).
* Patient has an intact meniscus (maximum 1/2-resection).
*Patient has a stable knee joint or sufficiently reconstructed ligaments. If not, ligament repair has to be done within 6 weeks to the planned cartilage treatment (ACT/microfracture).
*Patient has free range of motion of the affected knee joint or *10 degrees of extension and flexion loss.
*Patient has a defect of grade III or IV according to the ICRS classification.
*Patient has a maximum baseline score of 60/100 on the 2000 IKDC subjective knee evaluation.
*Patient is willing and able to give written informed consent to participate in the study and to comply with all study requirements, including attending all follow-up visits and assessments and postoperative rehabilitation regimen.

Exclusion criteria

Only selected (preoperative) exclusion criteria have been listed below. For the complete list see protocol.
Preoperative exclusion criteria:
* Patient is the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
* Patient is unable to undergo magnetic resonance imaging (MRI).
* Patient has prior surgical treatment of the target knee using mosaicplasty and/or microfracture (Note: prior diagnostic arthroscopy with debridement and lavage are acceptable). Anterior cruciate ligament repair are accepted, if the target knee is stable or a primary ACL reconstruction is performed within 6 weeks to the planned cartilage treatment (ACT/microfracture).
* Patient has radiologically apparent degenerative joint disease in the target knee as determined by Kellgren and Lawrence grade > 2.
* Patient has chronic inflammatory arthritis, and/or infectious arthritis.
* Patient has joint space narrowing >1/3 in the target knee when compared to the other knee or <3 mm joint space measured on X-ray.
* Patient has an instable knee joint or unsufficiently reconstructed ligaments. If ligament repair is necessary, the repair has to be performed within 6 weeks to the planned cartilage treatment (ACT/microfracture).
* Patient has malalignment (no valgus- or varus-deformity) in the target knee. In suspected

cases, the mechanical axis must be established radiographically through complete leg imaging during standing and in a.p. or rather p.a. projection.
The Mikulicz line is not allowed to deviate more than 5 mm of the Eminentia intercondylaris.
If alignment is necessary, surgery has to be performed within 6 weeks to the planned cartilage treatment (ACT/microfracture).
* Patient has prior surgical treatment of clinical relevance of the target knee.
* Patient has an osteochondral defect.
* Patient has bilateral lower limb pain or low back pain.
* Patient has a known systemic connective tissue disease.
* Patient has a known history of diabetes.
* Patient has a known autoimmune disease.
* Patient has a known immunological suppressive disorder or is taking immunosuppressants. Patient is currently systemically or intra-articularly taking steroids and/or has used steroids within the last 30 days prior to the planned arthroscopy (tissue harvest/microfracture).
* The patient has a known history of HIV/AIDS.
* The patient has a known history of Treponema pallidum (syphilis).
* The patient has an active hepatitis B or C infection with verified antigens. Patients with a cured hepatitis B or C infection and/or verified antibodies are not excluded.
* The patient has at the site of surgery an active systemic or local microbial infection, eczematization or inflammable skin alterations (including Protozoonosis: Babesiosis, Trypanosomiasis (e.g. Chagas-Disease), Leishmaniasis, persistent bacterial infections, like Brucellosis, spotted and typhus fever, other Rickettsiosis, Leprosy, Recurrent Fever, Melioidosis or Tularaemia).
* Patient has a known history of cancer.
* Patient has a known allergy against any of the ingredients of the IMP (NOVOCART® 3D plus).e.g. bovine proteins
* Patient is taking indomethacin or other NSAIDs as acute anti-pain and/or antiinflammatory medication.
* Patient has a known history of osteoporosis;
also patients with primary hyperparathyroidism, hyperthyroidism, chronic renal failure or patients with prior pathological fractures independent of the genesis.
* Patient has any degenerative muscular or neurological condition that would interfere with evaluation of outcome measures including but not limited to Parkinson*s disease, amyotrophic lateral sclerosis (ALS), or multiple sclerosis (MS).
* Patient has a body mass index (BMI) >35 kg/m2.
* Patient is a woman who is pregnant, lactating or anticipates becoming pregnant within 24 months after surgery.
* Patient is currently participating, or has participated in any other clinical study within 3 months prior to the screening visit.
* Patient has known current or recent history of illicit drug or alcohol abuse or dependence defined as the continued use of alcohol or drugs despite the development of social, legal or health problems.
* Patient has psychiatric or cognitive impairment that, in the opinion of the investigator, would interfere with the patient*s ability to comply with the study requirements, e.g., Alzheimer*s disease.
* Patient has any other condition, which, in the opinion of the investigator, would make the patient unsuitable for the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	NOVOCART® 3D plus
Generic name:	N3D plus

Ethics review

Approved WMO Date:	25-07-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	23-10-2014
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005798-22-NL
ClinicalTrials.gov	NCT01656902
CCMO	NL49836.000.14