NIHR | Innovation Observatory

# HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2019

# NOVOCART 3D for articular cartilage defects of the knee

| | | | |
|---|---|---|---|
| **NIHRIO ID** | 13181 | **NICE ID** | 10225 |
| **Developer/Company** | TETEC AG | **UKPS ID** | Not available |

| | |
|---|---|
| **Licensing and market availability plans** | Currently in phase III clinical trial. |

## SUMMARY


NOVOCART 3D is in development for the treatment of knee joint cartilage defects. Articular cartilage damage in the knee can be caused directly by acute injury, often as a result of sporting activity, e.g. repetitive trauma caused by high-impact sports. The condition may also arise without obvious trauma in individuals with defective cartilage. Damage of the articular cartilage does not heal on its own and can be associated with symptoms such as knee pain, knee swelling, knee locking and giving way of the knee joint, and may gradually develop into a chronic condition finally requiring total knee joint replacement.

NOVOCART 3D Autologous Chondrocyte Transplantation System is a biologic-device combination product composed of autologous (the patient's own) chondrocytes (cartilage producing and maintaining cells) seeded on a bioresorbable three-dimensional collagen scaffold, which is secured directly into the defect. The use of NOVOCART 3D involves two separate surgeries. In the first surgery, a small amount of knee cartilage is removed from the patient's affected knee and sent to the company to be processed for re-implantation. In a second surgery, the damaged area of the knee cartilage is cleaned and the sponge-like scaffold containing the autologous chondrocytes is implanted. If licensed, NOVOCART 3D will offer an additional treatment option for repair of articular cartilage defects of the knee.

# PROPOSED INDICATION

Repair of articular cartilage defects of the knee.[1-3]

# TECHNOLOGY

## DESCRIPTION

NOVOCART® 3D autologous chondrocyte transplantation system is a biologic device combination composed of *ex-vivo* expanded autologous chondrocytes seeded on a bioresorbable biphasic collagen scaffold.[4] This next generation concept for articular cartilage repair begins with three cartilage tissue biopsies taken from a non-weight bearing portion of the knee during an arthroscopic procedure. These biopsies are sent to the company where the chondrocytes are isolated and expanded. During the manufacturing, the cells are minimally passaged to prevent de-differentiation. At the end of the process, the chondrocytes are seeded onto the biphasic collagen scaffold.[3] NOVOCART 3D is therefore regarded as a patient individual medicinal product.[a]

NOVOCART 3D is currently in clinical development for the treatment of articular cartilage defects of the knee, undergoing pivotal clinical trials. In phase III clinical trials (NCT01957722 and NCT01656902), the patient's own chondrocytes, held within the three-dimensional scaffold, are applied directly into the defect. The use of NOVOCART 3D involves two separate surgeries. In the first surgery, a small amount of knee cartilage about the size of a pencil eraser is removed from the affected knee and sent to TETEC´s manufacturing facility to be processed for re-implantation.[a] During a second surgery, approximately three weeks later, the damaged area of the knee cartilage is cleaned and the sponge-like scaffold containing the autologous chondrocytes is implanted into the prepared space of the defect.[1,2,4]

## INNOVATION AND/OR ADVANTAGES

Articular cartilage has minimal endogenous ability to undergo self-repair. Matrix-assisted articular chondrocyte transplantation leads to better patient-reported outcomes in cartilage repair compared with currently available techniques, such as microfracture.[5] The architecture of the scaffold device is a defining feature of NOVOCART 3D. The scaffold consists of a porous sponge-like compartment, which allows for homogeneous distribution of cells within the scaffold, and a layer of robust collagen membrane cover. The sponge-like part of the scaffold has an organized three-dimensional pattern of fibres sized to allow the chondrocytes to adhere to the scaffold without losing their signature shape. The robust collagen membrane layer protects the chondrocytes after implantation and allows for easier handling within the surgical site.[3]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

NOVOCART® 3D does not currently have a Central European Marketing Authorisation in the EU for any indication. [a]

Prior to an EMA Central European MA, NOVOCART® 3D currently is used in the UK as a specials and was used in clinical trials before. [a]

[a] Information provided by the TETEC AG.

For the German market, a license according to national legislation transposing the provision of Article 3 (7) of Directive 2001/83/EC (Hospital Exemption Scheme) into German law was granted for NOVOCART® 3D on 29 August 2014 (Reg. No.: PEI.A.11511.01.1) by Paul-Ehrlich-Institute (PEI), the national competent authority for ATMPs in Germany. License has been re-approved on 25 September 2017. [b]

For the Swiss market, NOVOCART® 3D was approved by the Swissmedic on 02 October 2014 and re-approved on 21 March 2019 with the marketing authorization number Swissmedic 58945. Marketing authorization holder for NOVOCART® 3D marketed in Switzerland is B. Braun Medical AG, Sempach, CH, a subsidiary of TETEC AG's parent company B. Braun. Regarding this product, TETEC AG is the contract manufacturer for B. Braun Medical AG. [b]

This technology is considered a combined advanced therapy medicinal product (ATMP).[6]

NOVOCART3D is currently in clinical development only for the treatment of articular cartilage defect, undergoing phase III clinical trials, aiming for a central EMA approval. [b]

# PATIENT GROUP

## DISEASE BACKGROUND

The head of the femur (condyles and trochlea), tibia and the backside of the patella (kneecap) are covered with articular cartilage, a type of hyaline cartilage. Hyaline cartilage is normally very smooth, promoting frictionless movements of the joints and also acting as a shock absorber. The cells within hyaline cartilage are called chondrocytes. They are responsible for producing and maintaining the cartilage matrix, formed mainly from collagen. Cartilage has no blood and nerve supply, and therefore has a limited potential to repair itself.[7]

Cartilage damage can be caused by injury or arthritis, or can occur spontaneously. Cartilage damage may also arise because of knee instability or abnormal unbalanced pressures, for example after injuries of the knee ligaments or menisci. Obesity may also promote knee cartilage damage. In young people the most common cause of hyaline cartilage damage are sporting injuries. Symptoms associated with the loss of hyaline cartilage include pain, swelling, instability and joint locking. In addition, damage to the cartilage and surrounding tissues can cause osteoarthritis and may require partial or total knee replacement surgery in later life. People who have a knee replacement have an increased mortality risk during the surgery.[7]

Cartilage injuries can significantly impact quality of life. Physical impairment caused by cartilage injuries may lead to significant limitations in daily and professional life and work status for people with physically demanding jobs and professional athletes, or even result in loss of employment.[7]

## CLINICAL NEED AND BURDEN OF DISEASE

There are no reliable estimates of the prevalence of symptomatic articular cartilage defects of the knee, although it is estimated that every year in the UK, around 10,000 people have cartilage damage serious enough to require treatment. The number of people with symptomatic cartilage defects suitable for autologous chondrocyte implantation is estimated to be between 200 and 500 people per year in the UK.[8]

[b] Information provided by the TETEC AG.

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

People with articular cartilage defects should be offered best supportive care. This includes advice regarding physical exercises, weight loss and pain management; physiotherapy, intra-articular corticosteroid injections, analgesics, offloading, and applying heat/cold or transcutaneous electrical nerve stimulation.[9]

## CURRENT TREATMENT OPTIONS

Current treatment options include relief of symptoms, knee lavage with or without debridement (removal of damaged cartilage) and procedures to re-establish the articular surface. Interventions that aim to re-establish the articular surface include marrow stimulation techniques (such as microfracture), mosaicplasty (also known as osteochondral transplantation) and implantation of healthy cartilage cells (chondrocytes), a technique known as autologous chondrocyte implantation. For larger lesions, osteotomy (realigning of the knee) and knee replacement would be the main options.[8]

## PLACE OF TECHNOLOGY

If licensed, NOVOCART 3D will offer an additional treatment option for repair of articular cartilage defect of the knee.

# CLINICAL TRIAL INFORMATION

| | |
|---|---|
| **Trial** | NCT01656902, EudraCT 2011-005798-22, AAG-G-H-1202; aged 14 to 65 years; NOVOCART3D Plus; phase III |
| **Sponsor** | TETEC AG |
| **Status** | Ongoing |
| **Source of Information** | Trial registry[2] |
| **Location** | EU countries and Switzerland. One investigational site in Exeter, UK[c] |
| **Design** | Randomised, two arms, open label study |
| **Participants** | N=263; aged 14 to 65 years; patients with localised, full-thickness articular cartilage defects of the femoral condyle (medial, lateral) or trochlea of the knee (2.0 – 6.0 $cm^2$) were enrolled in the study. |
| **Schedule** | Participants will be randomised and treated with NOVOCART 3D Plus (matrix-induced Autologous chondrocyte implantation=ACI-M) or with Microfracture technique according to Steadman (=MFx). The ratio ACI-M/MFx is 2:1. |
| **Follow-up** | All patients will be followed up for 5 years after NOVOCART 3D Plus transplantation or Microfracture technique with assessments at 3, 6, 12, 18, 24, 36, 48 and 60 months. |
| **Primary Outcomes** | The primary endpoint is the patient's functional outcome as measured by the change in the 2000 International Knee Documentation Committee (IKDC) subjective knee score from baseline to the 24-month follow-up assessment. |

[c] Information provided by the TETEC AG.

| | |
|---|---|
| **Secondary Outcomes** | Key secondary *efficacy* endpoints are<br>• Change from baseline to the 24-month visit in the IKDC objective physician score.<br>• Change from baseline to the 24-month visit in the Knee Injury and Osteoarthritis Outcome Score (KOOS).<br>• Proportion of treatment failures at month 24<br>• Change from baseline to the 24-month visit in the SF-36 to measure clinical utility and summarize health-related quality-of-life and cost-effectiveness.<br>• Surgical time (cut-to-suture time).<br><br>*Safety data*<br>All adverse events will be recorded and summarized. Event descriptions, onset and resolution dates, and relationship to the advanced therapy investigational medicinal product (ATIMP) and procedures will be recorded. Additionally, each event will be categorized by seriousness and intensity to facilitate complete safety reporting throughout the clinical study. Of particular interest are the following three classes of adverse events:<br>• AEs leading to subsequent surgical interventions<br>• Treatment failures<br>• Other treatment-related serious adverse events |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | Estimated primary completion date was in May 2019. |

| | |
|---|---|
| **Trial** | NCT01957722, AAG-G-H-1220; aged 18 to 65 years; NOVOCART 3D vs microfracture; phase III |
| **Sponsor** | Aesculap Biologics, LLC |
| **Status** | Ongoing |
| **Source of Information** | Trial registry[1], Company[4] |
| **Location** | USA and Canada |
| **Design** | Randomised, active-controlled, partially-blind study |
| **Participants** | N=233; aged 18 to 65 years; BMI below 40; inadequate response to conservative treatment, cartilage defect localised at the femoral condyle or trochlea; defect size between 2-6 $cm^2$; defect grade III or IV according to International Cartilage Repair Society classification; intact, functional meniscus; stable knee joint or sufficiently reconstructed ligaments; and patients able to receive magnetic resonance imaging (MRI). |
| **Schedule** | Participants will be randomised to one of the treatment arms:<br>1. NOVOCART 3D - combination product- biologic (autologous chondrocytes) /device (scaffold) implant. |

| | |
|---|---|
| | 2. Microfracture - surgical procedure which creates a marrow clot in the prepare cartilage defect. |
| **Follow-up** | Subjects will be followed for five years in total |
| **Primary Outcomes** | Co-primary endpoints consisting of changes from baseline:<br>• Knee injury and Osteoarthritis Outcome Score (KOOS) - Pain Subdomain score at 24 months post-treatment<br>• KOOS – Activities of Daily Living (ADL) Function Subdomain score at 24 months post-treatment |
| **Secondary Outcomes** | • Dual Threshold Responder Rate at 24 months: 10 point or greater improvement from baseline in both co-primary endpoints at 24 months<br>• Change from baseline in VAS Pain scale at 24 months.<br>• Change from baseline in total KOOS score at 24 months.<br>• Change from baseline in KOOS Symptom sub-domain score at 24 months.<br>• Change from baseline in IKDC subjective score at 24 months.<br>• Change from baseline in KOOS Sport and Recreation sub-domain score at 24 months. |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | Estimated primary completion date was in July 2019. |

# ESTIMATED COST

The cost of NOVOCART 3D is not known yet.

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal guidance. Autologous chondrocyte implantation using chondrosphere for treating symptomatic articular cartilage defects of the knee (TA508). March 2018.
- NICE technology appraisal guidance. Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee (TA477). October 2017.
- NICE interventional procedure guidance. Mosaicplasty for symptomatic articular cartilage defects of the knee (IPG607). March 2018.
- NICE interventional procedure guidance. Microstructural scaffold (patch) insertion without autologous cell implantation for repairing symptomatic chondral knee defects (IPG560). June 2016.

- NICE interventional procedure guidance. Arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee (IPG493). May 2014.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

## OTHER GUIDANCE

- German Society of Orthopaedics and Trauma (DGOU). Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group "Clinical Tissue Regeneration". 2016.[10]

# ADDITIONAL INFORMATION

TETEC AG / Aesculap Biologics LLC did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

# REFERENCES


1 ClinicalTrials.gov. *NOVOCART®3D for Treatment of Articular Cartilage of the Knee (N3D). Trial ID: NCT01957722.* Available from: https://clinicaltrials.gov/ct2/show/NCT01957722 [Accessed 14 August 2019].

2 ClinicalTrials.gov. *Phase III Study to Evaluate Safety and Effectiveness of NOVOCART 3D Plus vs. Microfracture in Knee Cartilage Defects (N3D). Trial ID: NCT01656902.* Available from: https://clinicaltrials.gov/ct2/show/NCT01656902 [Accessed 14 August 2019].

3 Aesculap Biologics LLC. *Matrix Supported Autologous Chondrocyte Transplantation.* Available from: https://www.aesculapbiologics.com/en/healthcare-professionals/novocart-3d.html [Accessed 14 August 2019].

4 Aesculap Biologics LLC. *NOVOCART 3D Autologous Chondrocyte Implant System U.S. Phase 3 Clinical Trial.* Available from: https://www.aesculapbiologics.com/en/healthcare-professionals/novocart-3d-clinical-trial.html [Accessed 14 August 2019].

5 Wylie JD, Hartley MK, Kapron AL, Aoki SK, Maak TG. What is the effect of matrices on cartilage repair? A systematic review. *Clin Orthop Relat Res*. 2015 May;473(5):1673-82. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25604876 10.1007/s11999-015-4141-0.

6 European Medicines Agency (EMA). *Scientific recommendation on classification of advanced therapy medicinal products.* Available from: https://www.ema.europa.eu/en/documents/report/scientific-recommendation-classification-advanced-therapy-medicinal-products-autologous-expanded_en-0.pdf [Accessed 14 August 2019].

7 National Institute for Health and Care Excellence (NICE). *Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) - Appraisal consultation document.* Available from: https://www.nice.org.uk/guidance/TA477/documents/knee-cartilage-defects-autologous-chondrocyte-implantation-id686-appraisal-consultation-document2 [Accessed 15 August 2019].

8 National Institute for Health and Care Excellence (NICE). *Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) - Final*

*scope*. Available from: https://www.nice.org.uk/guidance/ta477/documents/cartilage-defects-knee-autologous-chondrocyte-implantation-final-scope2 [Accessed 15 August 2019].

9 National Institute for Health and Care Excellence (NICE). *Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee*. Available from: https://www.nice.org.uk/guidance/ta477/resources/autologous-chondrocyte-implantation-for-treating-symptomatic-articular-cartilage-defects-of-the-knee-pdf-82604971061701 [Accessed 15 August 2019].

10 Niemeyer P, Albrecht D, Andereya S, Angele P, Ateschrang A, Aurich M, et al. Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: A guideline by the working group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Trauma (DGOU). *Knee*. 2016 Jun;23(3):426-35. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26947215 10.1016/j.knee.2016.02.001.

***NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.***