NOVOCART

Current surgical treatment for intervertebral disc degeneration, provides relief to the accompanying pain and disability but does not restore the biological function of the intervertebral disc.

NOVOCART™ Disc plus, an autologous cell compound for autologous disc chondrocyte transplantation, was developed to reduce the degenerative sequelae after lumbar discectomy or to prophylactically avoid degeneration in adjacent discs.

NOVOCART DISC treatment consists of a two step procedure. In the first step, the biopsy would be taken during a discectomy procedure that removes the region of herniated disc. The disc chondrocytes would be isolated and expanded and suspended into a hydrogel for implantation. The final product would be injected through the annulus into the nucleus pulposus. Once in place, the disc chondrocytes may help regenerate tissue for a healthier disc.

The product is the subject of a Phase 2 trial within the European Union.

The product’s main features are:

High vitality

Individually manufactured for each patient

Capable of synthesizing the important matrix components collagen Type-II and aggrecan

Capable of synthesizing important growth and differentiation factors

Exclusion of over-expression of dedifferentiation markers (collagen Type-I) and of cartilage-destructive inflammation mediators such as Interleukin-1ß

Use of GMP-compliant manufactured homologous serum

Use of a high-quality in situ polymerizable hydrogel, subjected to a validated quality control dependent on load No antibiotics or antimycotics

Biological disc reconstruction

The only procedure allowing for biological reconstruction of partially damaged disc tissue before massive degeneration occurs is the transplantation of in vitro cultivated chondrocytes from autologous disc tissue,or ADCT (Autologous Disc Cell Transplantation). ADCT is comparable to joint ACT (Autologous Chondrocyte Transplantation) in its biological mode of action and in its biotechnological aspects. In both cases, isolated from the biopsy material, the cultivated cartilage cells induced the desired reconstruction. One further special feature of NOVOCART® DISC is the hydrogel used, which fixes the cells in the damaged disc, and possesses a range of other important properties, such as being anti-inflammatory.

Description of ADCT with NOVOCART® DISC

Transplantation of the cultivated disc cells can take place three months after extraction by way of operation of the prolapsed disc. The relatively long period between tissue extraction and cell transplantation must be adhered to, to ensure that the protective fiber ring (annulus fibrosus) is fully healed following the intervention.

In a phase-I/II study, NDplus is being investigated for its clinical applicability, safety, and efficacy in the repair of herniated, nucleotomized discs, and of adjacent degenerated discs, if present. To date, autologous disc chondrocytes have not been transplanted into degenerative discs without previous disc herniation. As such, this was the first study to investigate a therapeutic as well as a prophylactic approach to treat degenerative discs of the lumbar spine [1)].

The NDisc trial is an ongoing multi-center, randomized study with a sequential phase I study within the combined phase I/II trial with close monitoring of tolerability and safety. Twenty-four adult patients were randomized and treated with the investigational medicinal product NDisc plus or the carrier material only. Rates of adverse events in Phase I of this trial were comparable with those expected in the early time course after elective disk surgery. There was one reherniation 7 months after transplantation, which corresponds to an expected reherniation rate. Immunological markers like CRP and IL-6 were not significantly elevated and there were no imaging abnormalities. No indications of harmful material extrusion or immunological consequences due to the investigational medicinal product NDplus were observed. Therefore, the study appears to be safe and feasible. Safety analyses of Phase I of this trial indicate a relatively low risk considering the benefits that patients with debilitating degenerative disk disease may gain [2)].

Trial

Study Design Allocation randomized Endpoint classification safety/efficacy study Intervention model parallel assignment Masking open label Primary purpose treatment Arm NDplus (Experimental) NOVOCART® Disc plus (Autologous Disc Chondrocyte Transplantation System) novocart® disc plus Autologous Disc Chondrocyte Transplantation System (ADCT) NDbasic (Placebo Comparator) NOVOCART® Disc basic (media with no active cell component) novocart® disc basic ADCT (Media with no active cell component) Sequestrectomy only (SC) (No Intervention) Sequestrectomy (standard of care) Primary Outcomes Measure Oswestry Disability Index (ODI) time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) to 12-months follow-up Oswestry Disability Index (ODI) time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) to 24-months follow-up Oswestry Disability Index (ODI) time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) to 60-months follow-up Secondary Outcomes Measure MRI-signal (disc height, disc volumetry, signal intensity) time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Oswestry Disability Index time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up VAS for back pain and leg pain time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Health-related quality of life as measured by the SF-36 time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Healthy Questionnaire EQ-5D time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to

60-months follow-up Neurological status time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Functional status time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Return to work (days) time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Analgesic Medication Use during the previous 14-day-time period time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 60-months follow-up Physician assessments of ease of transplantation time frame: transplantation Surgical parameters, including length of procedure time frame: Sequestrectomy and transplantation Prevalence of subsequent surgical interventions time frame: 12-months post-operation Any unanticipated adverse event time frame: Baseline assessment 1<45d pre-sequestrectomy up to 60-months follow-up at any scheduled and unscheduled visit Specific laboratory parameters according to product compatibility and availability: CRP, IL-6, LTE4 time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 1,5-months follow-up Histology of the tissue explant time frame: Sequestrectomy Gene expression by quantitative realtime PCR of expanded cells, and cell culture medium metabolites during expansion time frame: Transplantation Biomarkers of blood and urine samples (SOX9, MMP-3, collagen type I, collagen type II, collagen type X, IL-1, aggrecan, BMP receptor Ia, BSP-2, FLT-1, collagen crosslinks, and yet to be defined additional elements) time frame: Baseline assessment 1<45d pre-sequestrectomy, pre-transplantation (90 +/- 15d post-sequestrectomy) up to 24-months follow-up Eligibility Criteria Male or female participants from 18 years up to 60 years old.

Inclusion Criteria:

1. The patient has a disc herniation with back and/or leg pain (radicular pain)

2. The patient has an indication for sequestrectomy according to the guidelines of DGNC and DGOOC

3. The patient is between 18-60 years of age.

4. The patient is physically and mentally able to participate in the study, and is able to understand the study, its goals and the possible risk factors involved. The patient is willing and able to participate in the follow-up visit plan at the study site and is able to understand and to complete study-relevant questionnaires in German language.

5. The patient is sufficiently informed about this trial orally and in writing. S/he had enough time for consideration, is willing to participate in the study and gives her/his written in-formed consent.

6. The patient confirms that s/he did not participate in a clinical study 90 days prior study inclusion. S/he agrees to refrain from participating in another clinical study during the NOVOCART® Disc Study and for another 90 days after study termination

Radiological Inclusion Criteria

Patients must meet all of the following criteria to be considered for enrollment in the NOVO-CART® Disc study.

1. The patient has a single-level lumbar disc herniation

2. The patient has more than 50% remaining disc height in the herniated disc in comparison to unaffected discs in the lumbar spine. If all discs show degenerative signs, disc height has to be at least 5 mm

3. The patient has no obvious signs of osteophytes and no end plate sclerosis in the lumbar segment to be treated with NOVOCART® Disc plus oder NOVOCART® Disc basic

Patients without adjacent degenerative disc (HD):

4. The adjacent proximal disc has no degenerative signs according to Pfirrmann Score stage 3 to 5.

Patients with adjacent degenerative disc (AAD):

4. The patients has additional degenerative signs in the proximal adjacent lumbar level ac-cording to Pfirrmann 3-4, but no more than 25% disc height reduction

Exclusion Criteria:

1. The patient has had a previous surgery at the lumbar level(s) and has been treated with NOVOCART® Disc plus oder NOVOCART® Disc basic.

2. The patient had a past recurrent disc herniation treated with sequestrectomy of the relevant disc.

3. The 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, multiple sclerosis, muscular dystrophy and myelopathic diseases of different causes.

4. BMI > 35 kg/m2

5. The patient has current or recent history of illicit drug, nicotine (more than 20 cigarettes per day) or alcohol abuse or dependence

6. CRP > 10mg/dl

7. The patient is pregnant, breastfeeding or actual planning to become pregnant. Female patients must be either at least two years postmenopausal or using one of the following means of birth control during the treatment phase, i.e. to transplantation

- surgical sterility

- double barrier methods, e.g. condom or diaphragm in combination with spermicide

- intrauterine contraceptive device

- bilateral vasectomy of sexual partner at least 90 days prior to enrolment in combination with barrier methods (e.g. condom or diaphragm)

- birth control pill

8. The patient has a history of known allergies or a suspicion of allergies to any of the NO-VOCART® Disc plus oder basic product components including hyaluronan, polyethylenglycol or albumin

9. Immune defects or the affinity for infections of known or unknown causes

10. The patient has a active systemic or local microbial infection, eczematization or inflammable skin alterations at the site of surgery (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).

11. The patient is unable to undergo magnetic resonance imaging (MRI)

12. The patient has a history or a suspicion of a disease with chronically inflammable character, as rheumatoid arthritis, gout, pseudo-gout, metabolic bone diseases, Crohn's disease, ulcerative colitis, lupus erythematosus, or other autoimmune disorders

13. Known osteoporosis

14. The patient has a primary hyperparathyroidism or hyperthyroidism, has chronic renal failure or has had previous fragility fractures.

15. Systemic connective tissue or collagen disease

16. Hereditary ocular degenerations with unclear diagnosis, retinopathies based on connective tissue-defined causes, macular corneal dystrophy, (based on the fact that the human cornea expresses cartilage specific proteins as essential functional elements and thus may serve as an indicator for paralleling degenerative events in various cartilaginous tissues)

17. The patient has immune suppression

18. The patient has a history of blood coagulation disease of different genesis, including known haemorrhagic diathesis of unknown cause

19. The patient had undergone chemo or radiotherapy within the past 5 years, or had any cancer other than non-melanoma skin cancer treated with curative intent within the past 5 years

20. Known diabetes, drug treated

21. Ulterior concomitant diseases or functional impairments of specific organs, which exclude study participation by the assessment of the investigator

22. The patient is a prisoner

Radiological Exclusion Criteria

• 1. The patient has apparent degenerative changes in the lumbar spine as determined by Modic Changes 2-3 2. The patient has one or more dysplastic vertebral bodies within the lumbar spine 3. The patient has a sacralised lumbar vertebra LWK5 at the level to be treated with NOVOCART® Disc plus oder NOVOCART® Disc basic 4. The patient has previous or acute spondylodiscitis 5. Segmental instability (spondylolisthesis > 5 mm) or translation

> 3 mm 6. The patient has a isthmic spondylolisthesis, ankylosing spondylitis or

spondylolysis 7. The patient has lumbar scoliosis (> 11° deformation). 8. The patient has previous trauma, discography or any other surgical intervention at the lumbar spine .

9. The patient has previous compression or burst fracture at the level(s) to be treated with NOVOCART® Disc plus or NOVOCART® Disc basic 10. The patient has a central spinal canal stenosis with evidence of a narrowing of < 8 mm (by MRI, sagittal) 11. The patient has a spinal tumor 12. The patient has metabolic bone disease 13. The patient has facet ankylosis or severe facet degeneration. 14. The patient has a lumbar kyphosis

Intra-surgery (tissue explant/sequestrectomy) Exclusion Criteria

1. Extensive damage of the Anulus, which subsequently poses a significantly greater risk of recurrence.

Exclusion criteria determined after tissue explant/sequestrectomy

1. HIV infection

2. Treponema pallidum (syphilis) infection

3. active hepatitis B or C infection

Exclusion Criteria prior Transplantation/Implantation

1. Recurrent disc herniation after surgery and prior transplantation/implantation.

Additional Information Official title A Prospective Randomized Multicentre Phase I/II Clinical Trial to Evaluate Safety and Efficacy of NOVOCART® Disc Plus Autologous Disc Chondrocyte Transplantation (ADCT) in the Treatment of Nucleotomized and Degenerative Lumbar Discs to Avoid Secondary Disease Principal investigator Hans-Joerg Meisel, Professor Description This is a classical Phase II study with an implicated Phase I part. The Phase I/II combination study is a non-confirmatory study aimed at gathering preliminary clinical information on NOVOCART® Disc plus used in a new indication in the repair of a herniated disc. It will be conducted in a prospective, multicenter, unmasked, clinical trial including 120 subjects randomized to NOVOCART® Disc plus (NDplus, 60 subjects), media NOVOCART® Disc basic with no active cell component (NDbasic, 36 subjects) and to standard of care (SC) sequestrectomy as control (24 subjects). 24 patients will be enrolled in Phase I of the study (12 NDplus, 12 NDbasic) and 96 patients in Phase II (48 NDplus, 24 NDbasic, 24 SC).

All subjects will be evaluated at 1.5-, 3-, 6-, 12-, 24-, 36-, 48-months post-t0 examination in the SC study arm and 1.5-, 3-, 6-, 12-, 24-, 36-, 48-months post-t5 examination in the NDplus and NDbasic study arms, and then 5 years post-t0/t5 to collect long-term clinical data. Efficacy measurements for functional improvement will be evaluated among NDplus, NDbasic and SC. Physiological effects observed from MRI measurements will be compared between appropriate treatments depending on expected treatment mechanisms. Safety data of NDplus will be combined with NDbasic to contrast against SC on procedure related risks and NDplus against NDbasic and SC together on graft-related adverse experiences.

To optimize the usefulness of clinical information, data collected in the study may be analyzed and reviewed continuously. Early findings may be used to modify the study design when deemed appropriate and acceptable by the Sponsor's medical advisors. Data-driven adaptive actions include but are not limited to stopping enrollment early. The Sponsor will inform regulatory bodies, Ethic Committees, and investigators before implementing study design modifications.

Cells and tissues collected from this study will be used in other in vitro-controlled experiments aimed at developing and validating known and novel biologic markers to quantify cell quality in the context of identity, purity and potency. Prognostic values of these biologic markers will be examined by correlating them with clinical data collected in this study.

The study will follow each subject for a total of five years post-t0 examination in the SC study arm and post-t5 examination in the NDplus and NDbasic study arms to obtain long-term performance data.

Patients must have a single-level acute disc herniation with an indication for an elective sequestrectomy. They may further have corresponding disc degeneration in the proximal adjacent segment (Pfirrmann Score Stage 3-4). A total of 120 adults will be enrolled in this study.

Each patient will remain in the study for 5 years post t0/t5 examination to complete the planned follow-up phase. It is expected to take 6 years and five months to collect all required data for this study. Trial information was received from ClinicalTrials.gov and was last updated in April 2016. Information provided to ClinicalTrials.gov by Tetec AG.

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Tschugg A, Michnacs F, Strowitzki M, Meisel HJ, Thomé C. A prospective multicenter phase I/II clinical trial to evaluate safety and efficacy of NOVOCART Disc plus autologous disc chondrocyte transplantation in the treatment of nucleotomized and degenerative lumbar disc to avoid secondary disease: study protocol for a randomized controlled trial. Trials. 2016 Feb 26;17(1):108. doi: 10.1186/s13063-016-1239-y. PubMed PMID: 26920137; PubMed Central PMCID: PMC4768412.
2)
Tschugg A, Diepers M, Simone S, Michnacs F, Quirbach S, Strowitzki M, Meisel HJ, Thomé C. A prospective randomized multicenter phase I/II clinical trial to evaluate safety and efficacy of NOVOCART disk plus autologous disk chondrocyte transplantation in the treatment of nucleotomized and degenerative lumbar disks to avoid secondary disease: safety results of Phase I-a short report. Neurosurg Rev. 2017 Jan;40(1):155-162. doi: 10.1007/s10143-016-0781-0. Erratum in: Neurosurg Rev. 2017 Jan;40(1):177. PubMed PMID: 27567635.