Study Protocol Title: A Prospective, Open-Label, Multicenter Pivotal Study to Evaluate the Safety and Efficacy of GelrinC® for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle: A Comparison to Historical Control Microfracture

Published: 07-02-2018
Last updated: 13-04-2024

To demonstrate the superior clinical efficacy of GelrinC on pain and function for the treatment of symptomatic focal articular cartilage defects of the femoral condyle in comparison to microfracture historical control at 24 months post-surgery.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Tendon, ligament and cartilage disorders
Study type	Interventional

Summary

ID

NL-OMON47786

Source
ToetsingOnline

Brief title
SAGE

Condition

- Tendon, ligament and cartilage disorders

Synonym
cartilage defect, cartilage lesion

Research involving
Human

Sponsors and support

Primary sponsor: Regentis Biomaterials Ltd
Source(s) of monetary or material Support: industry

Intervention

Keyword: Articular Cartilage Defects, femoral condyle, GelrinC

Outcome measures

Primary outcome

Co-primary efficacy endpoints:

Superiority will be declared if GelrinC is superior to microfracture on both

co-primary endpoints.

1. Change from baseline in KOOS)Pain score at 24 months.

2. Change from baseline in Knee Osteoarthritis Outcome Score (KOOS) Function in

daily living score at 24 months

Secondary outcome

Secondary Confirmatory Endpoints:

1. Change from baseline of Overall KOOS excluding "Function, Sports and

Recreational Activities" subscale at 24 months.

2. Change from baseline of Overall KOOS score at 24 months.

3. Modified MOCART score at 24 months.

4. Response (Yes/No) at 24 months on the KOOS Sports subscale, where *Response

= Yes* is defined as an improvement of at least 10 points on the scale from

baseline. The resulting rate in GelrinC will be compared to that of

microfracture historical control.

Additional Secondary Efficacy Endpoints:

5. Change from baseline in overall KOOS and individual subscales at 12, 18, 36,

48 and 60 months post-surgery.

6. Change from baseline in International Knee Documentation Committee (IKDC)

Subjective Knee Evaluation Form at 12, 18, 24, 36, 48 and 60 months

post-surgery.

7. Change from baseline in Short Form 12 (SF-12) at 12, 18, 24, 36, 48 and 60

months post-surgery.

8. Change from baseline in Visual Analogue Scale (VAS) at 12, 18, 24, 36, 48

and 60 months post-surgery.

9. MOCART and T2 mapping scores at 6, 12, 24 and 60 months post- surgery.

10. Rate of revisions throughout 24 months post-surgery.

Study description

Background summary

Articular cartilage is the smooth, glistening tissue that covers the sliding surfaces of bones within a joint. When cartilage is healthy, the bones are able to glide over each other, reducing friction and allowing a person pain-free movement. When cartilage becomes damaged due to trauma, significant pain and limited movement may severely impact a person*s normal ability to function in life. In the USA alone, more than 500,000 procedures are performed yearly for cartilage-related injuries.
Focal cartilage defects can adversely affect a patient*s quality of life with symptoms severely limiting their everyday activities. Heir et al2 have reported that patients with focal cartilage lesions suffer from pain and functional impairment and their quality of life is affected to the same extent as older patients scheduled for total knee replacement. Since adult cartilage has a poor intrinsic capacity for repair damage that is left
untreated may result in further degeneration eventually requiring knee replacement surgery. There is also data suggesting that repetitive cartilage injury may lead to osteoarthritis (OA) later in life.

Current treatment for cartilage defects involves one of the following five techniques:
1. Palliative: arthroscopic debridement, lavage and chondroplasty.
2. Intrinsic repair enhancement: Marrow stimulation such as microfracture or drilling.
3. Whole tissue transplantation: osteochondral autograft or allograft.
4. Cell-based repair: These treatments involve the implantation of either autologous or allogeneic cartilage cells which have been cultured to increase their number and then are implanted either with or without a supporting scaffold.
5. Cell-free scaffolds. These are typically three-dimensional matrices made of biodegradable biomaterials that are implanted into chondral or osteochondral defects.
Of these, typically palliative treatment is performed for lesions with ICRS grading of I-II while the remaining techniques are used for lesions with ICRS grading of III-IV. Palliative strategies (such as debridement and lavage) attempt to remove the mechanical sources of pain, but do not result in lesion fill. Approximately 60-70% of all cartilage procedures are palliative procedures. Intrinsic repair enhancement using marrow stimulation fills the lesion with fibrocartilage. It is estimated that about 20-30% of procedures involve marrow stimulation. Whole tissue transplantation such as mosaicplasty relies on the implantation of fully formed osteoarticular constructs into a chondral or osteochondral defect. Cell-based repair is generally performed in two stages: an initial biopsy is taken from an unaffected region of the joint to provide chondrocytes, which is then expanded in the laboratory followed by re-implantation of these cells in a second surgical procedure. Only approximately 5% of all cartilage procedures are cell-based. Acellular or cell-free scaffolds provide a framework onto which autologous cells, principally mesenchymal stem cells (MSCs) from the subchondral bone beneath the defect, may attach, differentiate and develop into new functional tissue

The pursuit of an optimal treatment for symptomatic articular cartilage defects in the knee joint remains elusive. The promise of cell-based procedures has not been realized and adoption is slow due to the complexity and risks of two surgical procedures, high costs and challenging regulatory pathways. Marrow stimulation or *microfracture*, although the recognized standard of care, results in the formation of fibrocartilage, which has been shown to provide only short term symptom relief for patients.
A new approach has emerged that involves the combination of microfracture with a biomaterial scaffold, such as GelrinC. Various acellular technologies are currently being used to augment microfracture12*16 and reports indicate improved clinical outcomes and a reduction in complications and adverse event rates. Long-term durability and sustained clinical outcomes have yet to be demonstrated and to date no acellular scaffold has been approved for distribution in the United States.

GelrinC is intended as a simple, off-the-shelf treatment for cartilage repair. It is provided to the physician as a ready-to-use liquid which is applied to a cartilage defect following a standard microfracture procedure. It is then cured in situ using UVA light to form a resorbable implant conforming to the shape and depth of the defect.
Early in the GelrinC product development, Regentis performed a series of pre-clinical studies. The first study in osteochondral defects (OCDs) in sheep (Report IL-013-02-2005) was designed to determine the formulation of GelrinC, while the later studies, performed in osteochondral (Report 89592) and chondral (microfracture) (Report 89593) defects in goats, assessed the safety, efficacy and degradation kinetics of GelrinC. These animal studies demonstrated that GelrinC is safe and that the newly formed cartilage following GelrinC treatment has properties similar to normal cartilage tissue.

The animal studies were followed by a multi-center pilot clinical study in Europe and Israel. A total of 56 patients were treated in the study. Clinical outcomes demonstrated a significant reduction in pain and improvement in function starting at 6 months and continuing to 24 months and beyond. Moreover, morphological assessment and T2 mapping suggest that the GelrinC procedure results in regenerated hyaline-like tissue with excellent maturation and collagen organization similar to normal cartilage.
The proposed GelrinC pivotal clinical study has been designed to compare the safety and efficacy of GelrinC with patient level data from historical control microfracture, the standard of care for the treatment of cartilage lesions. Based on the pilot clinical study
results, it is expected that the proposed pivotal study will demonstrate superior clinical outcome for GelrinC as compared to microfracture.

Study objective

To demonstrate the superior clinical efficacy of GelrinC on pain and function for the treatment of symptomatic focal articular cartilage defects of the femoral condyle in comparison to microfracture historical control at 24 months post-surgery.

Study design

Multicenter, open-label, controlled, non-randomized, double arm trial with a prospective treatment arm (GelrinC) and a historical control arm (microfracture).
GelrinC prospective treatment arm: patients will undergo an arthroscopy for evaluation purposes, followed by lesion debridement, standard microfracture procedure and GelrinC implantation.
Microfracture historical control arm: patients who were randomized to receive microfracture treatment as part of a prospective multicenter randomized controlled trial on a similar study population.

The patient ratio for the study will be 2:1 (2 prospective patients treated with GelrinC for each historical patient treated with microfracture). The follow-up schedule for the GelrinC arm will be similar to the one performed for the historical control, including a post-operative rehabilitation program.
Patients will be screened for eligibility. If found eligible the patient will undergo arthroscopy, inclusion/exclusion criteria will be confirmed and the GelrinC procedure will then be performed.
Patients will be followed-up at 2 and 6 weeks, 3, 6, 12, 18 and 24 months until the primary endpoint is reached and then will continue to an extended long term follow-up at 36, 48 and 60 months.
Patients will be requested to complete patient self-reported questionnaires (KOOS, 2000-IKDC Subjective, SF12 and VAS) at screening and at each visit from the 6 month post-operative visit onwards. At each follow-up visit, patients will be clinically evaluated by the surgeon. Follow-up MRI scans will be performed at 6, 12, 24 and 60 months in order to evaluate the morphology and quality of the repair tissue by MOCART and T2 mapping, respectively. The patient will also undergo a 12-month rehabilitation program starting immediately after the surgery.

Intervention

Test device: GelrinC.
The GelrinC precursor is composed of 4.5% w/w polyethylene glycol diacrylate (PEG-DA), <1% w/w denatured human fibrinogen (DHF) and 0.1% w/w photo-initiator in phosphate buffered saline (PBS) solution.
Amount implanted:
The GelrinC procedure is performed only once in each patient in a single surgical procedure. Implanted GelrinC volume depends on the size of the defect and is estimated to be between 1 and 2 ml.
Method of implantation:
Following a standard microfracture procedure, a mini-arthrotomy is performed and the liquid GelrinC solution is applied into a defect of the femoral condyle using the GelrinC accessory kit. The GelrinC solution is then UVA-cured into a solid implant in-situ.

Control treatment: Microfracture surgical procedure (historical control).
The control treatment is a standard arthroscopic microfracture procedure using standard and commonly available surgical tools.

Study burden and risks

The following are the main types of risks that may reasonably be anticipated with the GelrinC products procedure (i.e. device or procedure related):
* Allergic reaction to GelrinC components, arthrofibrosis, synovitis, erythema, effusion, infection, inflammation, arthralgia, patellofemoral pain syndrome, tearing or displacement of GelrinC, hypertrophy and injury to adjacent tissue

due to misuse of surgical accessories, viral or prion contamination.
* Risks related to the local anesthesia/nerve block used in the surgical procedure (e.g.,stinging sensation at the injection site, temporary weakness or paralysis of the affected area, convulsions, cardiac arrest, death)
* Risks related to the orthopaedic surgery, regardless of GelrinC products (e.g.,postoperative bleeding, persistent swelling, postoperative infection, phlebitis
(blood clots), pulmonary embolus, knee ligament injury, meniscal re-tear, compartment syndrome, reflex sympathetic dystrophy, tourniquet palsy, vessel injury, nerve injury, synovial fistula, and equipment failures)

The following are the benefits that may reasonably be expected for the GelrinC products procedure:
* Substantial reduction in pain
* Substantial improvement in function
* Substantial improvement in quality of life
* Regenerated tissue is hyaline-like, decreasing the chance for re-operation
* GelrinC products implantation procedure does not preclude or hinder subsequent procedures, if so required

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

1. Patient signed written informed consent.
2. Age between 18 and 50.
3. Patients must be skeletally mature.
4. Single, contained, symptomatic cartilage lesion of the knee predominantly located on the femoral condyle.
5. ICRS grade III or IV lesion.
6. Lesion size between 1 and 5 cm2 post debridement, less than or equal to 2.5 cm in diameter.
7. BMI *35.
8. Contralateral knee is asymptomatic, stable, fully functional and not medically treated.
9. Agree to actively participate in a strict rehabilitation protocol and follow-up program.
10. Agree to use pain medication only according to the following instructions: NSAIDs or combination preparation (of paracetamol/acetaminophen with codeine or similar max 4g/day) must be discontinued 2 weeks prior to baseline and 6, 12, 18, 24, 36, 48 and 60 month visits. Paracetamol/acetaminophen mono preparation (max 4g/day) must be discontinued one week prior to baseline and 6, 12, 18, 24, 36, 48 and 60 month visits.
11. Females of childbearing potential are willing to use a proven method to prevent pregnancy during the 24 months post-GelrinC procedure;Intra-operative confirmation:
12. Single contained symptomatic lesion located on the femoral condyle of the femur graded as ICRS III or IV with less than 5 mm of bone loss below the subchondral plate.
Note: Concurrent Grade I and II defects are allowed on the condyle, patella, tibia or trochlea with the exception of kissing lesions. These asymptomatic lesions
should remain untreated (or may be treated with debridement only) at the time of the arthroscopy and/or mini-arthrotomy.
13. Defect size between 1 - 5cm2 post debridement and less than or equal to 2.5 cm in diameter.
14. Lesion is fully visible and accessible with the GelrinC accessory kit.

Exclusion criteria

1. Presence of an additional Grade III or IV symptomatic lesion.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data (this includes but not limited to any chronic debilitating systemic disease, any other unstable cardiac or pulmonary disorders).

3. The target lesion is a patellofemoral cartilage lesion.
4. Target lesion in the femoral condyle is positioned posteriorly to the posterior horn of the meniscus and cannot be accessed by the GelrinC accessory kit.
5. Recent Osteochondritis Dissecans (OD) within 1 year of baseline visit.
6. Subchondral sclerosis.
7. Advanced osteoarthritis (Radiographic Atlas of OA grade 2-3).
8. Untreated ACL and/or PCL deficiency or complex ligamentous instability of the knee.
9. Meniscal transplant (previous/present).
10. Previous ipsilateral meniscal arrows or sutures (if not resorbed).
11. Current untreated meniscal tear.
12. A previous meniscal resection was:
Within the last 6 months, OR
Resulted in remnant that is less than 5mm at the narrowest region, OR
Resulted in nonfunctional root attachments.
13. Previous tendon repair or ligament reconstruction within the last 6 months.
14. Clinically relevant compartment misalignment exceeding 5° (according to x-ray).
15. Kissing lesions (symptomatic and asymptomatic).
16. Failed Mosaicplasty or ACI or MACI or any other cartilage repair product
17. Microfracture performed less than 1 year before baseline visit.
Note: prior diagnostic arthroscopy with debridement and lavage is acceptable.
18. Received Hyaluronic acid intra-articular injections into the afflicted knee within three months of baseline visit.
19. Received Corticosteroids intra-articular injections into the afflicted knee within the last three months of baseline.
20. Taking specific OA drugs, such as chondroitin sulfate, diacerein, nglucosamine, piascledine, or capsaicin within two weeks of the baseline visit.
21. Taking intramuscular or oral corticosteroids within two weeks of the baseline visit (inhalation corticosteroids are allowed).
22. Chronic use of anticoagulants or patients who have any coagulation disorder
Note: patients receiving low dose aspirin, temporary anti-platelet therapy or other anticoagulant medication should discontinue these medications per standard surgical procedure practice).
23. Known sensitivity to acrylic agents (or any of the components of GelrinC).
24. Participation in concurrent or previous clinical trial within three months of the baseline visit.
Note: participation in observational clinical trials is allowed.
25. Pregnant or breastfeeding.
26. Subjects with known HIV, Hepatitis A, Hepatitis B, Hepatitis C, syphilis or any other immune deficiency disease.
27. Malignancies:
- Current or prior malignancy of the affected limb.
- Current or prior malignancies in the body other than the affected limb within the last 5 years.
28. Alcohol or drug (including medication) abuse.
29. Subjects with documented uncontrolled diabetes (i.e. symptomatic, hyperglycemia that cannot be medically managed, fasting blood glucose level above 300mg/dL, and/or frequent swings between hyperglycemia or hypoglycemia).

30. Any concomitant painful or disabling disease of the spine, hips or lower limbs that would interfere with evaluation of the afflicted knee.
31. Any clinically significant or symptomatic vascular or neurologic disorder of the lower extremities.
32. Any evidence of the following diseases in the target joint: septic arthritis, inflammatory joint disease, gout, recurrent episodes of pseudogout, Paget*s disease of bone, ochronosis, acromegaly, hemochromatosis, Wilson*s disease, primary osteochondromatosis, heritable disorders, collagen gene mutations.
33. History of autoimmune disease or inflammatory arthropathy, such as rheumatoid arthritis, systemic lupus, active gout, septic or reactive arthritis including any history of a positive ANA blood test or chronic use of immunosuppressant.
34. Current diagnosis of osteomyelitis.
35. Screening blood result showing values of liver enzymes (SGOT, SGPT, alkaline phosphatase) that are twice as much as the upper limit of normal
value, or any other blood result that in the clinical investigator's opinion is important clinically.
36. CRP level > 10 mg/l.
Note: If CRP level exceeds the allowed limit, test can be repeated and patient will be reevaluated for eligibilty.
37. Patient is involved in a personal litigation (e.g., Workers Compensation lawsuit) that relates to knee treatment or surgery

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-07-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	GelrinC
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	07-02-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
CCMO	NL61710.068.17