Sterile allogeneic Spongioflex® allograft as partial meniscal replacement after incomplete meniscal loss, an investigator-initiated trial.

Study protocol from

January 5th 2024

NCT06376422

Protocol Full Title:	**Sterile allogeneic Spongioflex® allograft as partial meniscal replacement after incomplete meniscal loss, an investigator-initiated trial.**
Protocol Number:	EU-CT-2023-508271-36-00
Version:	Version 5 (Version 1-4 was an own template)
Amendment Number:	Not Applicable
Amendment Scope:	Not applicable
Compound Number(s):	SUB184038
Compounds Name(s):	Human Cancellous Bone (Spongioflex®)
Trial Phase:	Phase 4, Post-market authorization safety and efficacy study
Short Title:	Spongioflex® for partial meniscal replacement
Sponsor Name and Address:	Dr. Sven Behrendt Praxis für Knie- und Schulterchirurgie Hoher Wall 14 44137 Dortmund Deutschland Tel.: 0231 8626064
Manufacturer Name and Address	The Manufacturer of the substance is different from the sponsor DIZG (Deutsches Institut für ZeII- und Gewebeersatz) gemeinnützige GmbH Haus 42 Köpenicker Str. 325 D-12555 Berlin Deutschland
Regulatory Agency Identifier Number(s)	EU Trial Number: EU-CT-2023-508271-36-00
Sponsor approval Date	Sponsor is identical with Investigator

Sponsor/investigator Signatory

Dr. Sven Behrendt 05. Jan. 2024
Principal Investigator and Sponsor

Medical Monitor Name and Contact Information:
Medical Monitor Institution will be selected dependent on availability after approval of the study.

Report Serious Adverse Events within 24 hours via E-mail
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1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Primary and Secondary Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate efficacy PROMs (KOOS, IKDC, VAS Pain Score) are evaluated	Improvement of PROMs (KOOS, IKDC, VAS Pain Sore) 2 and 5 years after surgery compared to scores of the non-operated group and compared to pre-surgery scores

Secondary Objective	**Secondary Endpoint**
Safety of the patient	Type, frequency, and severity of treatment related to AEs and SAEs
Efficacy of the procedure	How many patients show a progression of osteoarthrosis up to TKA?
MRI image	2 and 5 years after inclusion in the study
Patient satisfaction	2 and 5 years after surgery

Overall Design

Several key aspects of the trial design are summarized below.

Intervention Model:	Parallel groups	**Population Type:**	Patients
Control:	Non-operated	**Population Diagnosis or Condition:**	Partial meniscal loss
Active Comparator:	N/A	**Population Age:**	Minimum: 18 Maximum: 60
Trial Intervention: Assignment Method	Patient decides if operated or not	**Site Distribution**	Single site

Number of Arms: 2 Arms

Blinding: Not Applicable (No blinding)

Number of Participants:

Number: 30 patients in the operated group and 10 in the non-operated group.

Arms and Duration

2 arms: operated /non-operated.

Duration:

- Patients operated:
  - Enrollment, Surgery (is the treatment), Follow-up:5 years,
- Patients not operated:
  - Enrollment, Follow-up:5 years,

Total duration of trial participation for each participant: Approximately 5 years

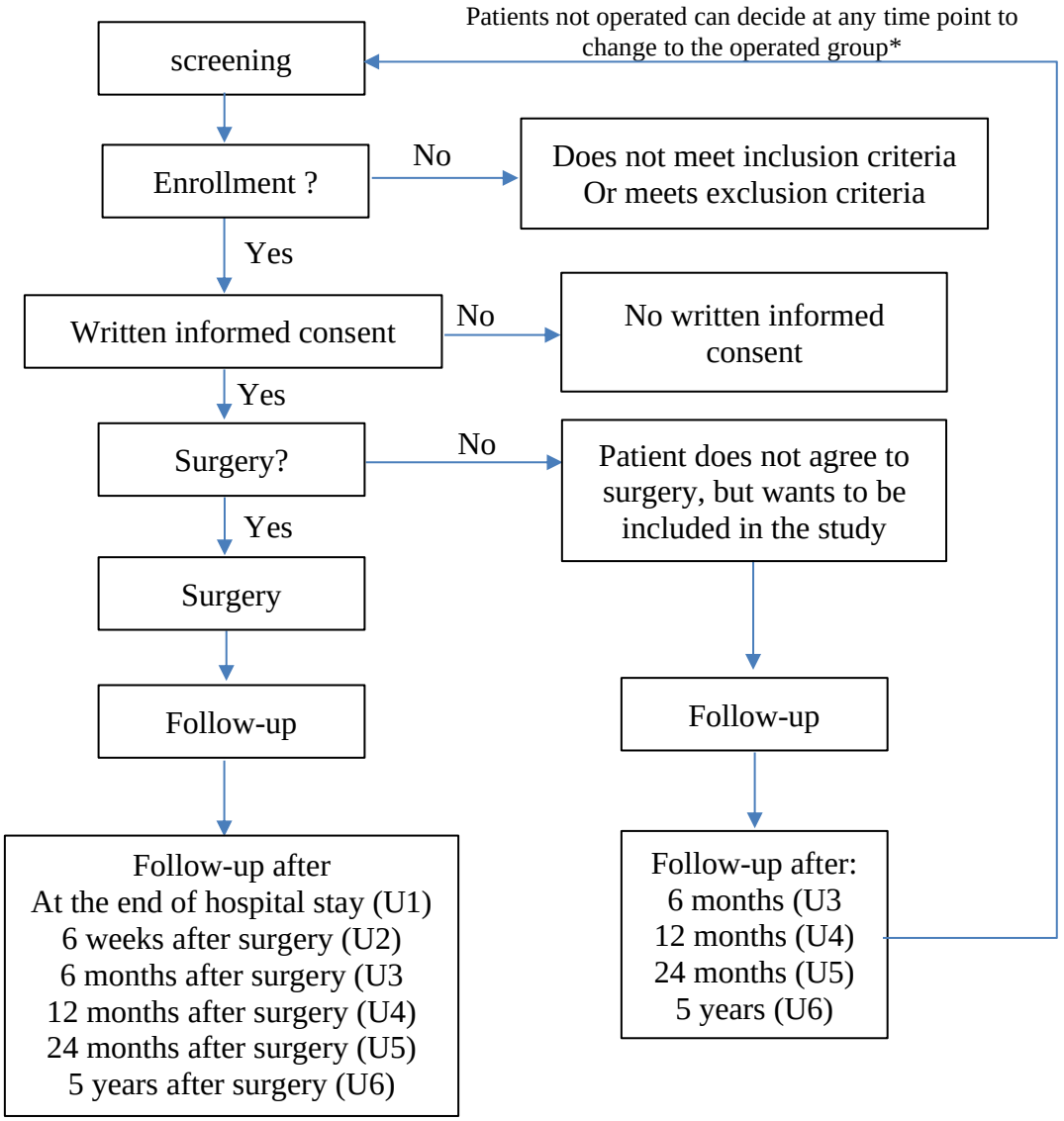
Dose: This is an orthopedic trial and there is no dose. The substance used is human cancellous bone (Spongioflex®) which exists in varied sizes (22x10x10 mm, 30x10x10 mm and 42x10x10 mm)

Rules/procedure: see Trial Schema

Committees:
N/A

Independent Committees:
N/A

1.2 Trial Schema



*The process: progression of osteoarthrosis is very slow. It will be very unlikely that more than 1 patient wants to change to the operated group within the 5 years of the trial. The same is true for progression to TKA. The possibility to change later in the operated group will take off the pressure from the patient to make the "wrong" decision now.

See point 1.3 Schedule of activities for details.

1.3 Schedule of Activities

Observation parameter in detail:

Parameter	Screening	Enrollment? yes/no	Surgery	Follow-up					
	(EU*)		OP	U1[#]	U2	U3	U4	U5	U6
date	V		V	V	V	V	V	V	V
surgeon	V		V	V	V	V	V	V	V
Medical history (age, gender, working status, co-morbidities)	V								
weight	V								V
height	V								V
BMI	V								V
Nicotine	V								V
Side	V								
Previous knee treatment	V								
Cartilage damage	V								
Leg axis misalignment	V								
Properties of the meniscus	V								
Sport	V					V	V	V	V
Scores (KOOS, IKDC)	V					V	V	V	V
VAS-pain Score	V					V	V	V	V
Diagnose	V								
Inclusion criteria	V	V							
Exclusion criteria	V	V							
Written informed consent		V	V	V	V	V	V	V	V
Pregnancy test			V						
Surgeon			V						
Time of surgery			V						
Graduation after Outerbridge [1]			V						
Way of Fixation			V						
Spongioflex®-properties			V						
Antibiotica			V						
Additional Procedures			V						
Complication			V	V	V	V	V	V	V
MR-image evaluation	V				V	V	V	V	V
Pain at rest				V	V	V	V	V	V
Pain when walking					V	V	V	V	V
Pain at sport						V	V	V	V
Pain medication	V			V	V	V	V	V	V
Reoperation					V	V	V	V	V
Patient satisfaction						V	V	V	V

*EU: screening visit; U1: at the end of hospital stay; U2: 6 weeks after surgery (± 4 days); U3: 6 months after surgery (± 1 months); U4: 12 months after surgery (± 1 months), U5: 24 months after surgery (± 1 months); U6: 5 years after surgery (± 3 months); [#]grey shading: this parameter will only be evaluated when operated

2 INTRODUCTION

2.1 Purpose of Trial

The menisci consist of fibrocartilage. They are partially (laterally more than medially) mobile parts of the joint surfaces and compensate for the incongruence of the femur and tibia. They reduce the joint pressure on the tibial plateau and the femoral condyles and help to stabilize the joint.[2] Due to this biomechanical relevance, the partial loss of the meniscus leads to arthritic changes in the medium and long term.[3-7] Suturing the torn meniscus is increasingly becoming the focus of knee surgery.[8] Degenerative torn menisci have a significantly poorer prognosis with regard to healing than traumatically torn menisci (e.g. meniscus damage associated with a cruciate ligament tear).[9]

Indications for partial meniscus replacement are symptomatic, degenerative, and irreparable damage to the inner and outer meniscus, possibly with early osteoarthritis of the compartments, as well as partial loss of the meniscus in the event of anterior knee instability in young, active patients, in which case simultaneous reconstruction of the anterior cruciate ligament should be performed. A prerequisite for a good clinical result after partial meniscus replacement is a stable knee without malalignment in the coronal plane. Partial meniscus replacement is not suitable in the case of axial deviation and knee instability, patients older than 60 years, advanced chondromalacia and degenerative changes in the affected compartment, an extension deficit of more than 3° compared to the opposite side or a knee flexion of less than 125°. Inflammatory arthritis or synovial inflammation of the knee and a BMI greater than 30 kg/m² are additional exclusion criteria.

Williams et al. 2007[10] could show, that 5 years after partial removal of the medial or lateral meniscus, despite an excellent functional result, 64% of patients showed medial and 33% lateral cartilage damage on MRI. This study highlights the considerable delay with which the symptoms occur despite already detectable arthritic changes.

Englund et al.[11] were able to show in a study that patients developed osteoarthritis significantly more frequently over a period of 30 months if they had meniscus damage than if they did not. Englund et al. [12] detected tibiofemoral osteoarthritis in 27% of patients 15 years after partial meniscus removal compared to 10% in a control group that had not undergone surgery.

In the case of incomplete meniscus loss, where the peripheral rim is sufficiently intact, defect filling is the only way to restore the lost substance and function of the meniscus.[13,14] In the past, an implant made of bovine collagen (Collagen Meniscus Implant (CMI), Stryker) or an artificial meniscus made of polyurethane (Actifit, 2med) was often used. The CMI has been withdrawn from the market by the manufacturer, so that no biological treatment alternative exists.

Schenk et al. [15] were able to show in a recent study for the CMI, consisting of bovine collagen that, despite a significant improvement in pain and function, the CMI is subject to a progressive shrinkage process over time. The studies mentioned above make it clear that partial replacement of the meniscus is necessary if preservation by meniscus suturing is no longer possible to prevent or postpone arthritic changes.

In the investigator-initiated study on which this application is based, a novel implant made from demineralized allogenic human cancellous bone (Spongioflex®, DIZG gGmbH Berlin) is to be implanted into the meniscus defect of the recipient knee. This transplant has sponge-like properties and therefore facilitates the ingrowth of cells from the surrounding meniscus. The IMP (Spongioflex®) is de-calcified and demineralized, it is hard, when dry, but soft when wet. In the knee the conditions are wet, thus it stays soft. It is pliable (Fig1) and can be easily sutured.

Figure 1: Spongioflex®

The manufacturer (DIZG gGmbH) did a study of cell ingrowth on Spongioflex®[16]. They describe that ingrowth of cells on Spongioflex® was observed after 28 days and these cells do not ossify[16].

Scotti et al. [17] summarizes 2013 the knowledge in respect to meniscal repair as follows:

> "In the last decade, striving for optimal restoration of meniscal tissue, the orthopedic surgeon`s armamentarium has been enriched by the use of biocompatible meniscus scaffold and meniscal allograft transplantation"[17]. "However, despite promising short-term results, none of the current strategies have demonstrated regeneration of a functional, long-lasting meniscal tissue and re-establishment of a proper knee homeostasis in the meniscectomised knee"[17]. "The rationale for using a cell-free biomaterial to replace part of the meniscus is based on repopulation of the scaffold by the host cells recruited from the synovium and the meniscal remnants, and subsequent tissue ingrowth which renders this approach cell-based after implantation. A mandatory prerequisite is the absence of both knee instability and malalignment"[17].

This section of the paper of Scotti et al.[17] describes exactly the need for a restoration of the meniscus. Furthermore it [17] defines exactly the features of a scaffold:

> " A biomaterial used as scaffold for meniscus tissue engineering purposes should present many features. In particular, the ideal meniscal scaffold should be (i) "cell-instructive", promoting cell differentiation and proliferation if cell-seeded, or cell migration if cell-free; (ii) "biomimetic", mimicking architecture, tribology and mechanical features of the native meniscus; (iii) resilient and resistant to withstand mechanical forces acting in the joint while cells produce ECM; (iv) biocompatible, not evoking any foreign-body reaction also with its degradation products; (v) slowly biodegradable allowing to be gradually replaced by biologic tissue; (vi) open, with high porosity, allowing diffusion of nutrients and catabolic substances; and (vii) easy to handle, to be sutured and to be implanted by the surgeon"[17].

Pereira et al. [18] describes that a meniscal implant, either for partial or total replacement should.

> "provide the biomechanical properties but also the biological features to replace the loss of native tissue. Moreover, these approaches include possibilities for patient-specific implants of correct size and shape"[18].

Spongioflex® fulfils all these demands described by Scotti et al.[17] and Peirera et al.[18] and it can be adapted in size and shape and thus is in the moment the optimal choice for partial meniscal replacement.

Dickerson et al. [19] describes that

> "the scaffold must have a high fluid conductance, concomitant with high porosity…. Porosity allows more rapid cell incorporation along the surface and through the thickness of the scaffold, promoting integration with the host tissue."[19]. "The scaffold must guide cells to regenerate all four zones of the tissue structure"[19].

This is the case of Spongioflex® it is porose and can guide cells. Scotti et al.[17] proposes 2013 to use CMI for partial meniscal regeneration, but this product is retracted from the market by now and they describe already the shrinking of the transplant[17]. Knee stability and an aligned knee are a requisite for the study proposed. Dickerson et al. [19] shows that new fibrocartilage tissue is formed on the demineralized end of the allograft. Results of Credille et al.[20] support these findings. It will not be ossified again[21]. Smith et al. [22] describes that

> "demineralized cancellous bone sponges are Food and Drug Administration-approved and commercially available products that have the potential to provide biologic and biomechanical augments for rotator cuff healing. The sponge can act as a scaffold for cellular attachment and proliferation" [22].

Credille et al. [20] showed in a recent publication that a biphasic interpositional cancellous allograft (BioEnthesis; Sparta BioPharma, Inc., Madison, NJ) can be used for rotator cuff repair. The allograft is

> "a porous scaffold for endogenous biological factor migration and thus potentially address the lack of enthesis recapitulation at the rotator cuff repair interface… while the demineralized layer supports soft-tissue ingrowth while acting as a "sponge" to hold bone marrow elements at the repair site"[1].

The group around Prof. Moroder [21] from the Charité has used Spongioflex® for glenoid repair. They describe that the transplant does not calcify again.[21] The glenoid is also no bony structure. They got an ethic vote (EA1/039/18) for using the same product in non-bone structures and could show successful restoration of the glenoid.
Sundar et al.[23] describes that the use demineralized bone matrix increased fibrocartilage when used for augmentation of rotator cuff repair. The used graft (Spongioflex®) provides a scaffold for cell migration of meniscal cells from neighbouring parts of the meniscus. The intended study will show that this kind of allograft is suitable for partial meniscal replacement because it allows cell migration and has enough porosity to allow fluid conductance [24]. As described by Wildemann et al. [25,26] sufficient growth factors are remaining in the demineralized bone matrix (Spongioflex®) to support new fibrocartilage formation. Scotti et al. [17] underlines the importance of growth factors for meniscal regeneration.

In summary from the literature, it can be concluded, that Spongioflex® is an attractive scaffold for partial meniscal repair because it is fully biological, it still has fibrocartilage inductive factors, allows cell migration, fluid conductivity, resists biomechanical forces, does not provoke immunoreactivity, it is adaptable in size and can easily be sutured. Partial meniscus replacement is an established surgical treatment for patients who have undergone partial meniscus removal[13,15,27,28], to lead to the ingrowth of cells and the regeneration of meniscus-like tissue.[29]

The purpose of this investigator-initiated trial is to evaluate whether the novel graft can prevent/reduce the disadvantages of the previously used replacement materials and shows better results than the group of patients, which were not operated. Since there is currently no alternative made of biological material to this product, this investigator-initiated trial is of great medical and economic importance. The otherwise following arthrosis [30] or knee prosthesis implantation (TKA) could be prevented or at least postponed. Initial clinical results are promising [31].
This surgical method contributes to both pain relief and functional improvement of the knee joint. The aim of this investigator-initiated study is to assess whether the novel transplant can prevent/reduce the disadvantages of the replacement materials used to date. As there is currently no alternative made of biological material to this product, the realization of this investigator-initiated study is of great medical and economic importance.
An important and sensitive parameter for assessing the postoperative function of the meniscus is the MRI image[32]. Genovese et al. 2007 were able to show in a categorization/classification which magnetic resonance image can be expected in the case of successful incorporation[32]. Several studies have shown that the known clinical knee scores (Lysholm, IKDC, KOOS, VAS pain) improve significantly after successful ingrowth of the meniscus implant [13,15,27,28,30].

Refer to the Section 1.2, Trial Schema, and Section 1.3, Schedule of Activities, for more information about the trial design.

2.2 Summary of Benefits and Risks

The expected benefits of the surgery outweigh the expected risks. The benefit of the surgery is expected to be improved knee functionality. The risk in the operated group are the normal risks of every surgery, like pain and redness of the interventional side, side effects of anaesthesia. The patients not operated do not have the risks applying to any surgery. For this patient group, there is an extremely limited possibility that the knee functionality will improve. Another benefit for both groups is the close follow-up of the knee functionality. The non-operated patients can, at any time point, decide to be operated.

Benefit Summary

Since only patients with partial meniscal loss are included, only through allogeneic partial meniscal implantation with Spongioflex® the lost function of the corresponding meniscus can be improved, and the graft will convert into endogenous tissue without recalcification[5]. For the patient group, which will not be operated there is a limited possibility that the meniscal function will improve. The psychological benefit for the operated group will be that they can better perform for their daily life duties.

The collagenous meniscus implant (CMI) has been withdrawn from the market. There is currently no alternative made of biological material. Spongioflex® does not affect the body's metabolism and does not influence the effect of medications the patient is taking. There are no restrictions for the patient for any medication. Allogeneic meniscal partial implantation is a standard orthopedic surgical technique that can be performed minimally invasively with arthroscopic support. Systemic side effects (e.g., transmission of infectious diseases) are not known after intra-articular application of freeze-preserved tissue grafts from the non-profit German Institute for Cell and Tissue Replacement (DIZG gGmbH). The grafts are sterilized using a validated sterilization procedure, and extensive donor screening is performed in accordance with regulatory requirements.

A case report[31] shows that the procedure was performed with no complications.

The benefit to society is that gonarthrosis will be postponed as well as TKA and thus the patient is able to work under better conditions, and longer before invalidity.

The hospital, where the procedure was performed, is available 24h/7days a week when problems occur.

Risk Summary and Mitigation Strategy

Trial-specific Discussion of Intervention Risks and Mitigations

There is a risk that even though the partial meniscal replacement is performed, the knee functionality will not improve. Strict inclusion and exclusion criteria should limit the number of cases without a benefit (see inclusion and exclusion criteria). The treatment would be the same, participating or not on the trial. Study specific is to fill the questionnaires at the planned visits (IKDC and KOOS, CRF).

Trial-specific Discussion of Procedure Risks and Mitigations
The procedure risks are the risk of any surgery for the operated group. The non-operated group does not have any surgical risk. They have the risk that the knee functionality will deteriorate. Due to the close follow-up, also for these patients, they can minimize this risk by deciding to change into the operated group.

Trial-specific Discussion of Other Risks and Mitigations
There are no other risks. There are no comparators, challenge agents or medical devices.

Overall Benefit: Risk Conclusion
The overall risk is very low, because partial meniscal replacement is an established operative procedure.

There are the normal risks applying to any surgical procedure. For the non-operated group, there are no surgical risks.
The benefit for the surgical group is the possibility of improvement of knee functionality. The benefit for the non-operated group is the close follow up to monitor the properties of the meniscus. This will help to decide to switch to the surgery group. The risks are assessed at least once a year for up to 2 years. After this treatment related risks are not expected. The 5-year visit is scheduled to verify the properties of the meniscus and to evaluate the exploratory outcome of progression of osteoarthrosis up to TKA.

3 TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1 Primary Objective + Associated Endpoint and Estimand

Primary Objective	**Primary Endpoint**
To evaluate efficacy of the procedure	Improvement of PROMs (KOOS, IKDC, VAS Pain Score) 2 and 5 years after surgery compared to scores of the non-operated group and compared to pre-surgery scores.

Primary Estimand (Variable): Difference in PROMs after 2 and 5 years
Endpoint: 2 and 5 years after surgery/enrollment, or progression to TKA
Treatment: varies with the group chosen by the patient (operated or not operated)
Population: male and female patients between 18 and 60 years
Intercurrent event: progression of osteoarthrosis up to TKA, lost to follow up, premature death, the patient wishes to change to the operated group after a certain time (The process: progression of osteoarthrosis is very slow. It will be very unlikely that more than 1 patient wants to change to the operated group within the 5 years of the trial. The same is true for progression to TKA. The possibility to change later in the operated group will take off the pressure from the patient to make the "wrong" decision now.)
Population-level summary: The primary objective is to compare the PROM change from baseline between the operated and non-operated group after 2 and 5 years. The difference in obtained PROMS will be evaluated.

Estimand Description: The Estimand are the Difference in PROMs. This includes specific knee scores (IKDC, KOOS) and the VAS-Pain Score. IKDC and KOOS have values between 0 and 100 and the higher they are as better the function of the knee. The VAS Pain Score has values between 0 and 10 and the higher the score the higher the pain.

3.2 Secondary Objective + Associated Endpoint and Estimand

Secondary Objective	**Secondary Endpoint**
Safety of the patient	Type, frequency and severity of treatment-related AEs and SAEs .
Efficacy of the procedure	How many patients show a progression of osteoarthrosis up to TKA?
MRI evaluation	Outerbridge graduation, size of meniscus, number of patients with extrusion, size of extrusion after 6 weeks, 6 and 12 months (for operated patients) and after 2 and 5 years, comparison between the operated and the non-operated group
Patient satisfaction	very pleased, pleased, not pleased, very unsatisfied in the operated group after 2 and 5 years.

Secondary Estimand(Variable): Safety of Patient: Number of AE and SAE, Efficacy of the procedure:

Number of patients with progression of osteoarthrosis up to TKA, MRI evaluation: Change in Outerbridge graduation from baseline and patient satisfaction.
Endpoint: 2 and 5 years after surgery/enrollment, or progression to TKA
Treatment: varies with the group chosen by the patient (operated or not operated)
Population: male and female patients between 18 and 60 years
Intercurrent event: progression of osteoarthrosis up to TKA; lost to follow up, premature death, the patient wishes to change to the operated group after a certain time (The process: progression of osteoarthrosis is very slow. It will be very unlikely that more than 1 patient wants to change to the operated group within the 5 years of the trial. The same is true for progression to TKA. The possibility to change later in the operated group will take off the pressure from the patient to make the "wrong" decision now.)
Population-level summary: The secondary objective is safety of the patient, efficacy of the procedure, MRI evaluation and patient satisfaction. Type, frequency and severity of treatment-related AEs and SAEs will be evaluated and how many patients show a progression of osteoarthrosis up to TKA, to compare the MRI image from baseline and patient satisfaction after 2 and 5 years.

Estimand Description
Safety of the patient and efficacy of the procedure: if AE, SAE or SUSARs are reported, the benefit-risk balance evaluation will be renewed, and it will be decided if the study will be continued.
MRI Image will be evaluated using the Outerbridge [1] graduation, the size of the meniscal defect and the meniscus itself, the MRI signal of the meniscus will be evaluated after a modified score after Genovese et al.[32] and if there is an extrusion and which size the extrusion has. Patient satisfaction will be categorized as: very pleased, pleased, not pleased, very unsatisfied and will be evaluated using the Chi-square test.

3.3 Exploratory Objective + Associated Endpoint and Estimand

Exploratory Objective	**Exploratory Endpoint**
How many patients show a progression of osteoarthrosis up to TKA	Progression of osteoarthrosis up to TKA

Exploratory Estimand (Variable): Progression of osteoarthrosis up to TKA
Endpoint: 2 and 5 years after surgery/enrollment
Treatment: varies with the group chosen by the patient (operated or not operated)
Population: male and female patients between 18 and 60 years
Intercurrent event: lost to follow-up, premature death
Population-level summary: the explorative objective is: how many patients have a progression of osteoarthrosis up to TKA, in the operated and non-operated group.

Estimand Description:
The number of patients with progressing of osteoarthrosis up to TKA will be evaluated using the Kaplan Meier estimator for time to event.

4 TRIAL DESIGN

4.1 Description of Trial Design

Description of Intervention Model
This investigator initiated; low intervention trial is performed with 2 groups. The intervention group is the group of patients who will be operated. The control group are the patients not willing to be operated. Due to the incidence of patients with partial meniscal loss in the last years in the private praxis of the principal investigator 30 patients in the operated group and 10 patients in the non-operated group will be recruited within 2 years of recruitment. The study will be performed to prove patient safety and efficacy of the procedure. The process of progression of osteoarthrosis is very slow. It will be very unlikely that more than 1 patient will be in this situation and wants to change to the operated group within the 5 years of the trial. The same is true for progression to TKA. The possibility to change later in the operated group will take off the pressure from the patient to make the “wrong” decision now.

Description of Trial Duration
The total trial duration will be 7 years. The recruitment period will be 2 years. Follow-up is 5 years. Depending on, if the patient will be operated or not, the time until surgery will add on these 5 years. The substance used (human cancellous bone) does not have a dose. It will be used in various dimensions.

Method of Assignment to Trial Intervention
This is a single centre trial. The initiator of the trial will perform the trail on its own. Due to the small number of patients included, the investigator will perform all visits on its own. There is no randomization. The patient decides if he/she will be operated or not. There is no blinding. A clinical monitor will perform data monitoring. There are no plans for a data monitoring committee due to the small number of patients and small number of data recorded. Bias is minimized by investigating the MRI images after a standardized protocol. The PROMs are filled in by the patient without the help of the investigator. The analysis will be performed by the investigator using statistical software. Patients from the non-operated group can transition to the operated group at any time. There are no rules for transition.
An interim analysis is planned after 2 years. See details in section 9.7
There will be no sample collection during the trial. In the moment there is no extension of the trial over the 5 years planned.

4.2 Rationale for Trial Design

Rationale for Intervention Model
The comparison of the 2 groups (operated/non-operated) are chosen, because this gives an instant possibility to compare the knee functionality with and without surgical treatment.

Rationale for Duration
Only after 2 years the result can be evaluated. Biological processes in the meniscus are slow. Shrinkage of the transplant as described for CMI can occur later (up to 2 years). But normally after 2 years the remodelling process is finished. For this reason, close follow-up is performed for up to 2 years.

Rationale for Endpoints
The endpoints are the knee functionality after 2 and 5 years, the safety of the patient and the efficacy of the method. If the benefit-risk balance changes the investigator evaluates if the study will be continued.

Progression of osteoarthrosis up to TKA are additional end points for single participants.

Interim Analysis
An interim analysis will be performed in 2 years. If the benefit-risk balance changes or the safety of the patient or the efficacy of the procedure is not any mor given, the study will be stopped.

4.2.1 Rationale for Comparator

There is no comparator, the control group is the group of non-operated patients

4.2.2 Rationale for Adaptive or Novel Trial Design

There are no adaptive or novel trial design

4.2.3 Other Trial Design Considerations

There are no other trial design considerations.

4.3 Access to Trial Intervention After End of Trial

If the trail shows benefit for the patient the procedure will be performed after the trial as standard procedure by the investigator.

4.4 Start of Trial and End of Trial

The start date of the trial will be as soon as the approval for the study will be obtained. The end point will be the last visit of the last patient enrolled in the trial.
Firs act of recruitment is the screening:
The recruitment of patients for the investigator-initiated trial takes place during the consultation hours of the study centre. Since patients are specifically assigned for partial meniscus implantation, patients are already informed about the investigator-initiated trial at the time of appointment. During the first visit the inclusion and exclusion criteria are evaluated. If the patient qualifies for participation in the study based on the inclusion and exclusion criteria, he/she will be informed about the therapeutic procedure of partial meniscus implantation with Spongioflex® and the planned investigator-initiated trial (planned visits, data protection, etc.) will be explained. Patients also receive an information sheet explaining the surgical procedure, the advantages and disadvantages, the risks, and the follow-up treatment. After a sufficient reflection period, the patient must sign the consent form for participation in the investigator-initiated trial and the data protection declaration. Without these written consents, inclusion in the investigator-initiated trial cannot take place. After the signatures, the patient is included in the investigator-initiated trial. In accordance with standard clinical practice, the usual risk information for the surgical procedure is provided, for patients who decided to be operated. For the control group (not operated patients) the follow up visits are explained. This is conducted based on the information sheet customary in the respective hospital. In this form, patients are usually informed about the procedure, the treatment alternatives, the risks, and the aftercare. Woman are treated in the same way. Spongioflex® does not affect the body's metabolism and does not influence the effect of medications the patient is taking, thus there is no need for special female treatment option. There is no restriction for medication taken by the patient.
Pregnant women are excluded from surgery but can join the non-operated group.
Minor patients are not included.

The investigator-initiated trial may only be terminated prematurely for ethically relevant, i.e., medical/ scientific reasons.

Premature exclusion of a patient from the study:

- If, during the waiting period for the Spongioflex® graft, changes in the patient's state of health occur that constitute a contraindication for partial meniscal implantation (e.g., infection of the knee joint, tibial plateau fracture), the physician conducting the study must withdraw the patient from the investigator-initiated trial if this appears reasonable and necessary for medical reasons.

Premature termination of the entire study: Reasons for premature termination of the investigator-initiated trial include:

- If the identifiable risks outweigh the expected benefits.
- If an unreasonable risk to patients is apparent.
- If unexpected serious adverse events (SAE); Suspected Adverse Drug Reaction (SADR) occur that are causally related to the insertion of the meniscal implant, they will be reported to the EudraVigilance database. Patients will be followed up until the SAE or SUSAR/SADR is solved, if necessary, in the hospital, otherwise as outpatient.
- IF SUSARs are reported, a new benefit/risk balance evaluation will be performed and after the analysis it is decided if the study will be continued.

If the investigator-initiated trial is terminated or suspended prematurely, the study director will inform the regulatory authority(ies) of the termination or suspension and provide a statement to that effect. The Ethics Committee will be promptly notified and provided with a detailed written explanation for the study director's termination or suspension of the investigator-initiated trial, as specified in the applicable regulatory requirements. If the investigator-initiated trial is terminated or suspended prematurely for any reason, study participants will be notified immediately.

Patients can stop the participation of the study at any time, without giving the reason for it.

The investigator and the sponsor are the same person, He has the right to decide if there will be an early site closure or if the study will be prematurely terminated. For further details see 10.5 (Early site closure or trial termination) for criteria and responsibilities related to early site closure or trial termination.
In the event of premature termination or suspension of the investigator-initiated trial, irrespective of the reason, further follow-up of patients will continue according to standard clinical practice.

5 TRIAL POPULATION

5.1 Selection of Trial Population

This trial is performed on adult patients with a maximal age of 60 years. The enrollment criteria are carefully selected to increase patient safety and efficacy of the procedure. Patients must have a partial loss of the lateral or medial meniscus and a lateral or medial joint line pain. In this trial there are no drugs used. The human cancellous bone (SUB184038) is used in various dimensions to suite the defect. The progression of this partial loss ist the total loss of the meniscus, which is treated with total meniscal allograft replacement and when the cartilage is severely damaged a TKA is the only treatment option. The patients treated in this trial are mainly young active patients who want to continue their sport and daily life. Thus, to try to improve knee functionality is the goal of the partial meniscal replacement.

5.2 Rationale for Trial Population

The rational for choosing this trial population is that this part of the population has this kind of diagnosis, and it must be treated as soon as possible. Additional measures are taken for leg axis misalignment and ACL rupture. For the efficacy of the procedure the leg must have a normal alignment and must be stable.
No children or patients, who are unable to consent for themselves, or those that may respond to the trial intervention differently are included. There is no restriction on medicine taken by the patient because the allograft does not have systemic actions.
Screening is performed via MRI. There must be a sufficient standing peripheral rim, so that the procedure can be performed. No laboratory tests or genetic tests are necessary for the screening. When the operation is decided later on, the usual laboratory tests are performed as for every surgery, not being a trial. Only after successful screening the patient will be enrolled. Subgroup possible will be sex (female versus male) and smoker versus non-smoker if enough power is generated to do statistical calculations.

Individuals who do not meet criteria for trial eligibility will not be enrolled via protocol waivers.
or exemptions.

5.3 Inclusion Criteria

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Patients (male and female) with:
2. Partial loss of portions of the
    - lateral meniscus and lateral joint line pain

    OR
    - medial meniscus and medial joint line pain
3. sufficient standing of the peripheral rim, so that the procedure can be performed
4. Age: 18-60 years
5. signed written informed consent to the study and to provide the scientific data in pseudonymized form

5.4 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this trial:

1. The presence of anterior cruciate ligament insufficiency which is not resolved by reconstruction of the anterior cruciate ligament within 16 weeks after partial meniscal implantation.
2. Axial deviation (>2° varus or valgus)
3. realignment osteotomy not performed within 12 weeks

4. advanced cartilage damage (grade III according to ICRS) and osteoarthrosis in the affected compartment (grade III according to Kellgren and Lawrence [33])
5. Extension deficit of more than 3° compared to the opposite side or a knee flexion of less than 125°
6. inflammatory arthritis or synovitis on the treated knee
7. BMI greater than 30 kg/m²
8. <18 years, >60 years
9. Chronic pain patients
10. only for patients who will be operated:
    a. with increased anaesthesiologic risk, e.g., with known or predicted difficult airway
    b. with increased risk of bleeding
    c. with increased risk of infection
    d. with necrotic, infected, or poorly perfused host sides
    e. history of allergic reactions
    f. acute hypersensitivity reactions to the IMP or any of its excipients
    g. pregnant woman

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

No meals and dietary restrictions.

5.5.2 Caffeine, Alcohol, Tobacco, and Other Habits

There are no restrictions to the intake of caffein, alcohol, or tobacco.

5.5.3 Physical Activity

Physical activity is restricted for the patients having an operation as follows: Rehabilitation consist of 5 weeks partial weight bearing, range of motion will be restricted for the first 3 weeks to 30 °flexion, 4th week 60 °, 5th week 90 °, then full range of motion exercises were allowed. Jogging is not allowed for 4 months and contact sport only after 6 months.

5.5.4 Other Activity

There are no restrictions to blood or tissue donation and sun exposure.
Driving is not allowed for operated patients for 8 weeks with manual transmission and when the right leg is concerned also for automatic transmission.
Heavy labour not for 3 months.

5.6 Screen Failures

Screen failures will be left in the study. The study will be performed after the principle: full analysis set. The principal investigator is performing the screening himself, thus screening failures will be limited.

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of Trial Intervention

The investigator-initiated trial is a "low-intervention clinical trial" according to Article 2(3)CTR. It will be conducted in accordance with the “FSA-Kodex” and the joint recommendations of the BfArM and PEI on the planning, conduct and analysis of investigator-initiated trials. The clinical trial will be conducted in compliance with the protocol, with the CTR regulation and with the principles of good clinical practice according to Annex I section D 17 (a) CTR 536/2014.

The IMP is SUB184038, human cancellous bone, auxiliary medicinal product (NIMP) is Cephazolin, 2 gr. one shot just before surgery, IMP and NIMP for the surgical group only.

Fig. 2 example of packaging and labelling.

The IMP can be stored at room temperature (fig. 2). The transplant must be re-hydrated at least 30 min before implantation in physiological injectable solution (Fachinformation point 4.2).

Intervention for the surgery group: As for any surgical procedure, the patient receives an antibiotic shot NIMP) just before surgery. The patient will be arthroscopically treated via the arthroscopic portal with implantation of a demineralized bone block (IMP: Spongioflex ®, appropriate size (DIZG gGmbH, Berlin, Germany)) as a partial meniscus substitute. The block will be adapted to the defect size and secured with 2-4 inside-out sutures (Etibond 0, Ethicon, Somerville, NJ). No dosing, the IMP has no systemic effect. The surgery (Intervention) will last between 60-90 minutes. The hospital stay is between 2-3 days after surgery. Follow-up visits: at the end of the hospital stay, after 6 weeks, after 6, 12 and 24 months and after 5 years for the operated group.
Non-operated group: no surgical treatment, no antibiotic shot, no visit at the end of the hospital stay, and no visit after 6 weeks. Follow-up visits after 6, 12 and 24 months and after 5 years.

Table 1: Trial interventions

Trial intervention	Operated group	Non-operated group
screening	yes	yes
enrollment	yes	yes
In-hospital surgery as summarized above with IMP and NIMP as defined above	yes	no
Follow-up includes MRI evaluation and IKDC, KOOS and VAS-pain-Score at each follow-up visit	yes	yes
at the end of hospital stay	yes	no
After 6 weeks	yes	no
After 6 months	yes	yes
After 12 months	yes	yes
After 24 months	yes	yes
...After 5 years	yes	yes

6.2 Rationale for Trial Intervention

Arthroscopy is an established method to treat meniscal lesions. This is the best way to protect the soft tissue and to minimize the risks for the patient. The IMP is a human cancellous bone block, which is hard when dry and has spongy soft properties when wet. It is sold in varied sizes. It can be sized in accordance with the defect size, it is pliable (important for shuttling through arthroscopic ports) and allows cell and fluid migration. The IMP has no systemic effect and thus does not have a dose. A case report [31] shows first promising results. The group around Prof. Moroder [21] from the Charité has used Spongioflex® for rebuilding the glenoid surface and were unable to demonstrate re-ossification on subsequent MRI scans up to 12 months and could show successful restoration of the glenoid. There are still sufficient growth factors in the IMP to initiate cell migration from surrounding tissue. Demineralized bone, as Spongioflex®, supports soft-tissue ingrowth [20]. See 2.1 purpose of trial for more details.
There is no dose and no regime, thus there is no rational for dose and regime.

6.3 Dosing and Administration

The size of the IMP will be estimated by MRI evaluation and approved with the measuring rod during surgery by the operating surgeon.
The IMP will only be handled by the orthopedic surgeon. The patient does not handle the IMP and not the NIMP, thus no instructions for the patients are needed.

6.3.1 Trial Intervention Dose Modification

There is no dose, thus there is no dose modification

6.4 Treatment of Overdose

There is no dose, thus there is no overdose

6.5 Preparation, Handling, Storage and Accountability

6.5.1 Preparation of Trial Intervention

The preparation of the IMP is only handled by the investigator of the trial. The size of the IMP will be adapted

due to the defect size. The re-hydration of the IMP will be 30 min prior use in physiological injectable solution as explained in the “Fachinformation” (attached as separate document). The NIMP will be applied I.V.

6.5.2 Handling and Storage of Trial Intervention

The IMP can be stored at room temperature up to the date indicated on the package. Handling follows the instruction in the “Fachinformation” and as describe under 6.2 and 6.5.1.

6.5.3 Accountability of Trial Intervention

The IMP and NIMP will only be handled by the investigator. Each patient does get only 1 IMP. Because the size will be adapted during surgery, he is able to order the IMP before knowing the patient’s defect. He has a storage of the IMPs (in the operating tract) of the available sizes to treat several patients without the need to order. He orders via the hospital, where the treatment is performed from the manufacturer. The product is available on the market for orthopedic surgeons with a prescription.

There is no return of unused products, the rest of the IMP, which is not implanted, will be disposed in the operating tract. One IMP is only allowed to use for 1 patient, even the remaining part would be big enough for treating another patient (Fachinformation point 6.6).

6.6 Participant Assignment, Randomisation and Blinding

6.6.1 Participant Assignment

The patient decides after screening on its own if he wants to be operated or not. For this reason, the patient decides to which group he will belong.

6.6.2 Randomisation

There is no randomization

6.6.3 Blinding and Unblinding

There is no blinding
Emergency Unblinding: Because there is no blinding there is no need for emergency unblinding.

6.7 Trial Intervention Compliance

Trial compliance is only for the follow-up-evaluation. It does not concern the IMP, because the IMP is placed at the surgery in the patient. The compliance is expected to be high with the restrictions regarding activity and the compliance with the visits. It is expected that maximal 20% of patients will be lost for follow up or withdraw their consent.

6.8 Concomitant Therapy

There are no restrictions to concomitant therapy. There is no medication/supplement restriction for the trial. The IMP has no systemic effect. The patient can take all medications, which he has already, and which will be additionally during the trial period. There are only restrictions on activity as explained in 5.5.3 after surgery in the operated group.

6.8.1 Prohibited Concomitant Therapy

There is no prohibited concomitant therapy.

6.8.2 Permitted Concomitant Therapy

Every other therapy is permitted during the trial.

Rescue Therapy

There is no rescue therapy. The patient who progress to osteoarthrosis or TKA would be excluded from data interpretation but would remain in the trial as the full analysis set principle is followed. This patient would be counted as failed treatment.
A withdrawal from the trial by the patient (after surgery) will only affect the follow-up data. Withdrawal before surgery will not generate follow-up data, but patient will still be left in the study due to the full analysis set principle. This does not lead to temporary discontinuation of the study.

6.8.4 Other Therapy

There can be physiotherapy to improve the return to daily life and sport.

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention

7.1.1 Criteria for Permanent Discontinuation of Trial Intervention

This is an orthopedic trial. The surgery is the start point and after the surgery there is no further treatment. There are only follow-up visits, which include an MRI (after 6 weeks, 6, 12, 24 months and 5 years in the operated group and after 24 months and 5 years in the non-operated group) and 3 questionnaires (IKDC and KOOS, CRF).
Criteria for permanent discontinuation for **single patients** from the trial are the following:

- Withdrawal of the informed consent
- lost to follow-up,
- premature death
- progression of osteoarthrosis up to TKA
- the patient wishes to change to the operated group after a certain time

When withdrawal of the informed consent, premature death or lost to follow-up occurs, data up to the point will be used. If progression of osteoarthrosis up to TKA occurs, the treatment is counted as treatment failure. These patients cannot continue the trial. Data up to the point will be used.
If the patient changes his decision and want to be operated at a later time point, the patient can continue the trial, but will be allocated to the other study arm. Data collected up to this point will be used in the first treatment group and then data will be generated in the second treatment group.

7.1.2 Temporary Discontinuation or Interruption of Trial Intervention

This is an orthopedic trial. The surgery is the start point and after the surgery there are no treatments. There are only follow-up visits, which include an MRI and 3 questionnaires (IKDC, KOOS, CRF)
If the patient cannot attend a post-surgical visit at the time envisaged it is possible to do the visit later/earlier. For this there are time ranges given which is as follows:

- U1: at the end of hospital stay (only for operated patients)
- U2: 6 weeks after surgery (± 4 days, only for operated patients)
- U3: 6 months after surgery (± 1 months, for operated patients, for non-operated patients only PROMs)
- U4: 12 months after surgery (± 1 months, for operated patients, for non-operated patients only PROMs)
- U5: 24 months after surgery (± 1 months)
- U6: 5 years after surgery (± 3 months)

If for any reason this time slots cannot be used by the patient e.g. because of a pandemic or another major event, then the next time slot will be used.
Thus, a temporary discontinuation of the trial is not a problem, because no treatment occurs after surgery, but should be avoided.

7.1.3 Rechallenge

Because the treatment is finished after the surgery, there is no re-challenge possible for patients in the operated group. Patients from the non-operated group can change to the operated group, but this is than no rechallenge, but the start of the trial as described under 1.2 Trial Scheme.

7.2 Participant Withdrawal from the Trial

This is an orthopedic trial. The surgery is the start point and after the surgery there is no further treatment. There are only follow-up visits, which include an MRI and 3 questionnaires (IKDC, KOOS, CRF). If a participant withdrawal his informed consent. If the patient is not compliant with the restrictions for rehabilitation after surgery (as described under 5.5.3), the investigator has the right to withdraw the patient from the trial. Data are used until the withdrawal.

7.3 Lost to Follow-Up

This is an orthopedic trial. The surgery is the start point and after the surgery there are no treatments. There are only follow-up visits, which include an MRI and 3 questionnaires (IKDC, KOOS, CRF). Follow-up-visits are at the end of the hospital stay, 6 weeks after surgery (both for operated patients only), and then for all patients: after 6, 12 and 24 months and after 5 years.
Lost to follow-up will occur because the trial population are mainly young active people. They will move for work or private reasons and may not finish the visits. In the number of patients for the trial lost to follow-up is included in the statistical calculations. The investigator will explain, when the informed consent is discussed with the patient, the importance of attending the follow-up-visits. If the investigator has the impression that the patient will not be compliant regarding the follow-up-visits, he will not include the patient in the trial.
When a patient is lost to follow up, the data up to the last visit attended will be used.

7.4 Trial Stopping Rules

If AE, SAE and SUSARs change the benefit-risk balance, there will be a new benefit-risk balance evaluation and after this evaluation it will be decided if the trial will be stopped.
If the safety of the patients is not any more given, the trial should be stopped.
The investigator expects a maximal 20% failure rate of the procedure. If the failure rate is higher a new benefit-risk balance evaluation must be performed and after the evaluation it must be decided if the trial continues.
The investigator also has the right to stop the trial. This could be because of the closure of the site. See 10.5 for details.

8 TRIAL ASSESSMENTS AND PROCEDURES

Assessment procedure is described in detail under 1.2 trial scheme and under 1.3 schedule of activities.

8.1 Screening/Baseline Assessments and Procedures

The recruitment of patients for the investigator-initiated trial takes place during the consultation hours of the study centre. Since patients are specifically assigned for partial meniscus implantation, patients are already informed about the investigator-initiated trial at the time of appointment.
During the first visit (Screening) an MRI is done and evaluated, the inclusion and exclusion criteria are verified. If the patient qualifies for participation in the study based on the inclusion and exclusion criteria, he/she will be informed about the therapeutic procedure of partial meniscus implantation with Spongioflex® and the planned investigator-initiated trial (planned visits, data protection, etc.) will be explained. Patients also receive an information sheet explaining the surgical procedure, the advantages and disadvantages, the risks, and the follow-up treatment. After a sufficient reflection period, the patient must sign the informed consent form for participation in the investigator-initiated trial and the data protection declaration. Without these written consents, inclusion in the investigator-initiated trial cannot take place. After the signatures, the patient is included in the investigator-initiated trial. At this time point the patient must decide if he wants to be operated or not. In accordance with standard clinical practice, the usual risk information for the surgical procedure is provided for patients who decided to be operated. This is conducted based on the information sheet customary in the respective hospital. In this form, patients are usually informed about the procedure, the treatment alternatives, the risks, and the aftercare. Woman are treated in the same way. Spongioflex® does not affect the body's metabolism and does not influence the effect of medications the patient is taking, thus there is no need for special female treatment options. There is no restriction for medication taken by the patient. For the control group (not operated patients) the follow-up visits are explained.
- Pregnant women are excluded from surgery
- Minor patients are not included

8.2 Efficacy Assessments and Procedures

The surgical procedure will be assessed at any time. The procedure should be successful in at least 80% of the patients. If there is a failure rate of more than 20 % the benefit-risk balance evaluation will be renewed. If the risk overweight’s the benefit of the surgical procedure, the trial will be prematurely terminated. For this reason, close meshed follow-up is scheduled to obtain sufficient information regarding the efficacy of the surgical procedure.

8.3. Safety Assessments and Procedures

This is a low intervention trial. This trial poses a minimal additional risk to subject safety compared to normal clinical practice (CTR, page 2 (11)).
As described under 8.2 there is a close-meshed follow-up schedule, for operated patients, which will also evaluate the patient’s safety. The highest risk that safety issues occur is during surgery. But the surgery is an established method. All safety measures will be taken during surgery as for every surgery, not being a clinical trial. The first visit at the end of the hospital stay is one of the safety measures for the patient. Before the patient leaves the hospital, the patient will be checked, if there are no issues which may affect his/her safety.
AE, SAE and SUSARs are recorded in the electronic patient chart and will be recorded in the CRF.
AE will only be recorded in the electronic patient chart and in the CRF. When AEs affecting the conduct of the trial and/or increasing the risk to the subject, the IRB/IEC should be promptly informed by a written

report.
SAE: because the investigator and sponsor is the same person in this trial, information to the sponsor is immediately. The SAE will be recorded in the electronic patient chart and in the CRF. Unless the protocol waives the notification, the investigator reports the SAE to the ethic committee and to the local authorities (Bundesoberbehörde) immediately but at least within 15 days, after becoming aware of it. If the investigator does not have all the information by then, the missing information must be submitted as soon as possible.
SUSARs: The investigator/sponsor shall inform the competent higher federal authority, the lead ethics committee, and the competent authorities of other Member States immediately, but at the latest within 15 days of becoming aware of a SUSAR. The deadline is reduced to 7 days if an unexpected serious adverse reaction is life-threatening or has led to death.
There are no laboratory investigations part of the trial.
There is no independent Data Monitoring Committee. Clinical monitoring will be performed from an independent clinical monitor for the safety of the patients. The extend and nature of the monitoring will be adapted due to Article 48 CTR.

8.3.1 Physical Examination

Physical examinations will be performed at each visit. Normal evaluations will not be recorded, only adverse events and complications.

8.3.2 Vital Signs

Vital signs are only recorded before and during surgery. The IMP has no systemic effect. For this reason, vital signs are recorded and not evaluated in the follow-up visits.

8.3.3 Electrocardiograms

Electrocardiograms are only recorded before and during surgery. The IMP has no systemic effect. For this reason, vital signs are not recorded and evaluated in the follow-up visits.

8.3.4 Clinical Laboratory Assessments

Clinical laboratory assessment will only be performed before surgery, due to normal medical praxis to prepare surgery. After the surgery, a laboratory assessment will only be performed, when AE (e.g. infections) are recorded or other events which need laboratory assessment. This will be due to routine practice of the hospital, where the patient is located or due to the practice of the investigator for such events and is not related to a special laboratory assessment due to the clinical trial

8.3.5 Suicidal Ideation and Behaviour Risk Monitoring

The diagnosis of partial meniscal defect is not life-threatening, thus suicidal ideation is not common for this kind of diagnosis. As described in 8.2, a close meshed follow-up is scheduled after surgery. The KOOS questionnaire includes questions about the quality of life. Discussion with the patient about the outcome of the KOOS questionnaire will point out possible suicidal ideation and will activate a closer follow up of the patient.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions of AE and SAE

AE definition: any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment CTR article 2 (32). There are

4 grades of AE: mild AE; moderate AE; severe AE and life-threatening AE or disabling AE.

SAE definition: any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death
Additional details and clarifications for AEs and SAEs are in Appendices 12.1 and 12.2

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

At each follow-up (at the end of the hospital stay, after 6 weeks, after 6, 12 and 24 months and after 5 years, for the operated group and after 6, 12, 24 months and 5 years for the non-operated group) AE and SAE are collected regularly. Since the patient can inform the investigator about AE, or SAE at any time, collecting AE and SAE are performed as soon as known by the investigator. After finishing the trial, the investigator is still reachable for the patient to inform him about any AE or SAE.

8.4.3 Identifying AEs and SAEs

At each follow-up AE and SAE are collected regularly. Since the patient can inform the investigator about AE, or SAE at any time, collecting AE and SAE are performed as soon as known by the investigator. After finishing the trial, the investigator is still reachable for the patient to inform him about any AE or SAE

8.4.4 Recording of AEs and SAEs

AEs and SAEs will be recorded in the electronic patient chart and in the CRF and in the adverse event log/serious adverse event log. Severity and causality and final outcome will be recorded.
Further details on assessing severity and causality of AEs and SAEs are in Appendix 12.3 and 12.4

8.4.5 Follow-up of AEs and SAEs

The adverse event log/serious adverse event log will follow-up all actions taken in respect to solving the adverse event or serious adverse event. Patient will be followed until the AE/SAE is solved either in the hospital or as an out-patient.

8.4.6 Reporting of SAEs

SAEs will be reported in the electronic patient chart, in the CRF and to follow-up in the SAE event log. All SAEs will be reported to the ethic committee and to local authorities (Bundesoberbehörde) at least 15 days after obtaining knowledge of the event. SAEs related to the IMP will be reported to the EudraVigilance Data base.
On the Webpage of the PEI there is a document
((https://www.pei.de/DE/arzneimittelsicherheit/gewebevigilanz/meldeformulare/meldeformulare-node.html
Form G1a) to be filled in for :" Meldung des Verdachts einer schwerwiegenden unerwünschten Empfängerreaktion im Zusammenhang mit der Übertragung von Gewebe, Gewebezubereitungen oder Stammzellen gemäß § 63i AMG" this form would be filled and send to the PEI.

8.4.7 Regulatory Reporting Requirements for SAEs

For this clinical trial, the sponsor and the investigator are the same person. The investigator/sponsor must report the following:
SAEs should be reported to the ethic committee and to the authorities (Bundesoberbehörde) immediately after knowledge of the event, but not later than 15 calendar days. Life threatening SAEs must be reported

within 24 h but at least 7 days after being aware of the case. Follow-up-reports must be submitted if the information in the initial submission is incomplete.

8.4.8 Serious and Unexpected Adverse Reaction Reporting

SUSARs which are fatal or life threatening, the sponsor should report at least the minimum information as soon as possible and, in any case, not later than 7 days after being aware of the case to the ethic committee and to the local authorities (Bundesoberbehörde). SUSARs which are not fatal, or life threatening are to be reported within 15 days to the ethic committee and to the local authorities (Bundesoberbehörde). SUSARs must be reported to the EudraVigilance date base electronically and to the PEI using the specified form.

8.4.9 Adverse Events of Special Interest

There are no adverse events of special interest expected.

8.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

Disease related events and outcomes, which will be not reported as AE or SAE will be: progression of osteoarthrosis up to TKA. This will happen when the treatment failed.

8.5 Pregnancy and Postpartum Information

8.5.1 Participants Who Become Pregnant During the Trial

A pregnancy test must be performed before surgery for female patients, who are able to become pregnant. The patient group without surgery does not have to do the pregnancy test. Patients not able to become pregnant (male patients, female after menopause) do not have to have a pregnancy test. After surgery, the patient can become pregnant without any risk for her safety or for the efficacy of the study. If a patient wants to change to the surgery group, a pregnancy test must be performed before surgery.
Pregnancy after surgery is not an AE.

8.5.2 Participants Whose Partners Become Pregnant

Participants, whose partners become pregnant is not an AE. The IMP has no systemic effect and thus does not affect reproductivity or child development. Pregnancy information of the partner will not be collected.

8.6 Medical Device Product Complaints for Drug/Device Combination Products

There is no medical device included.

8.6.1 Definition of Medical Device Product Complaints

n/a

8.6.2 Recording of Medical Device Product Complaints

n/a

8.6.3 Time Period and Frequency for Collecting Medical Device Product Complaints

n/a

8.6.4 Follow-Up of Medical Device Product Complaints

n/a

8.6.5 Regulatory Reporting Requirements for Medical Device Product Complaints

n/a

8.7 Pharmacokinetics

The IMP human cancellous bone has no pharmacokinetic action. It does not have systemic effects (Fachinformation point 5.1.

8.8 Genetics

No genetic information is recorded during the trial.

8.9 Biomarkers

No Biomarkers are collected during the trial.

8.10 Immunogenicity Assessments

There will be no immunogenicity assessment. The IMP is an authorized product and there are up to now no reports in respect to events regarding immunogenicity.

8.11 Medical Resource Utilisation and Health Economics

Medical resource utilization is minimal. The additional burden for the investigator is the explanation of the clinical trial to the patient and the filling of the documents related to the clinical trial.
The burden for the patient is the extended explication regarding the trial and the filling of the forms (KOOS, IKDC, CRF) during the visit. The patient must be compliant with the visit schedule, this could be an additional burden.
Regarding the health economics: Ther are no additional costs because of the trial. If the procedure shows efficacy and patient safety, the health system can save additional costs related to total meniscal transplantation or progression of osteoarthrosis up to TKA. Additionally, the patient can work longer and does not need or only needs later support from the government.

9 STATISTICAL CONSIDERATIONS

Data analysis complies with ICH E9 Guideline and ICH E9(R1) Guideline. This clinical trial is to confirm patient safety and efficiency of the procedure.
For this reason, as primary objective PROMs (IKDC, KOOS and VAS-pain score) will be evaluated before surgery/at the beginning of the trial and then starting at 6 months after surgery/beginning of the trial for the operated or non-operated group, respectively. The evaluation will be performed also after 12 and 24 months and after 5 years. A primary analysis will be performed 2 years after surgery/start of the trial.
At the beginning of the trial and prior to operation demographic and baseline data will be collected and summarized for both groups.
For safety, there will be an evaluation of complications, AE, SAE and SUSARs at each follow-up visit (at the end of the hospital stay, after 6 weeks, after 6, 12, 24, months and after 5 years, for the operated group). The number of AE, SAE and SUSARs will be recorded and evaluated at each visit. MRI evaluation starts at the follow-up visit 6 weeks after surgery for the operated group and 24 months after the start of the trial for the non-operated group. The evaluation of the MRI will be performed after a modified graduation of Genovese et al. [32]. Additionally, there will be the meniscal size evaluated and if there is an extrusion of the meniscus and how big the extrusion is. There will be a Kaplan-Meier-time to event curve for both groups regarding progression of osteoarthritis up to TKA. The analysis will be conducted on all participant data after 2 years and after 5 years.

9.1 Analysis Sets

Full analysis set will be performed.

PROMs:
Change from baseline for the PROMs (IKDC, KOOS, VAS-pain score) for the operated/non-operated group after 6, 12 and 24 months and 5 years and between groups.

Complications, AE, SAE and SUSARs:
The number of complications, AE, SAE and SUSARs will be evaluated at each time point and compared between the groups with Fishers exact test.

MRI evaluation:
Change in MRI evaluated using the Outerbridge [1] graduation, the size of the meniscal defect and the meniscus itself, the MRI signal of the meniscus will be evaluated after a modified score after Genovese et al.[32] and the number of patients with an extrusion and the size of the extrusion.

Patient satisfaction:
Patient satisfaction will be categorized as: very pleased, pleased, not pleased, very unsatisfied and will be evaluated using the Chi-square test.

Progression of osteoarthrosis up to TKA:
The number of patients with progression of osteoarthrosis up to TKA for both groups will be compared with a Kaplan-Meier time to event curve.

9.2 Analyses Supporting Primary Objective(s)

The PROMs (IKDC, KOOS, VAS-pain score) may be considered as continuous numerical data. The PROMs

will be summarized by sample size N, mean, standard deviation (SD), minimum, first quartile Q1, median, third quartile and maximum. Box plots will be used to provide a graphical overview. If the numerical data are normally distributed an independent t-Test can be performed, if they are not normally distributed, a Mann-Whitney-U-Test must be used. Statistically significant differences will be assigned when $p<0.05$.

9.2.1 Statistical Model, Hypothesis, and Method of Analysis

The change in PROMS from baseline in the operated and non-operated group will be compared by two-sided t-test for independent groups when data are normally distributed or with the Mann-Whitney-U-test.

The Null-hypothesis is that partial meniscal replacement does not improve mean PROMs for knee function in comparison to the non-operated group after 2 and 5 years.

The alternative hypothesis is that there that partial meniscal replacement does improve mean PROMs for knee function in comparison to the non-operated group after 2 and 5 years.

The PROMS should improve (Mean KOOS and IKDC should increase by at least 20 points, and VAS-pain score should decrease by at least 3 points, or to near zero, depending on the pre-surgical value).
Analysis of data will be performed by direct comparison of the groups at each time point and in comparison, to before surgery/start of the trial. Mean and standard deviation of the groups are compared. If there is a significant difference, the Null-Hypothesis will be rejected. Even when we have a loss of follow-up of 20% the power will still be 0.985. From our experience mean KOOS values presurgical are between 40-50 and between 50-60 for the IKDC, after treatment the expected improvement is to mean values between 80-90 for both scores. For the VAS-pain-score the presurgical mean value is around 4 and the post-surgical value is between 0 and 1. There is no risk of a type 1 error, because the values are measured several times over the follow-up period, thus there will be no false positive result. If the difference in the scores between pre- and post-surgery is lower than 18, the power is not big enough. Thus setting 20 as the difference for rejecting the Null-hypothesis is supported by enough power, even with only 8/24 patients in the respective group. The covariate could be smoking and sex. Smoking affects healing in general. It is not clear if there will be enough patients in each group to use these as confounders. Interactions will not be possible, because the treatment has no relation to any characteristic of the patient. There will be no adjustment made and no model fitting.

9.2.2 Handling of Intercurrent Events of Primary Estimand(s)

Intercurrent events are: progression of osteoarthrosis up to TKA, lost to follow up, premature death, the patient wishes to change to the operated group after a certain time. (as stated under point 3).
Data obtained until the event will be included in the analysis, last observation will be included in the evaluation. In case of progression of osteoarthrosis up to TKA the procedure will be noted as fail. Premature death will be treated as lost to follow-up. Lost to follow-up and premature death can be unrelated to knee problems. If the patient wishes to change the treatment group, data are collected for this treatment up to the last treatment. If more than 20 % of patients fail, the benefit-risk balance will be re-evaluated, and it will be decided if the trial will be continued.

9.2.3 Handling of Missing Data

If the patient withdraws his consent, data up to this date will be used for the analysis. The last observation carried out will be the end point. Patient will be reported as withdrawn.
Patients are not randomized and do not have therapy after surgery, they just have follow-up visits. There will be the full analysis set model for the analysis, thus all data from patients will be reported, which were

enrolled. If a patient is lost to follow up, the patient will be reported as this.
For patients with progressing of osteoarthrosis up to TKA, they will be recorded as failed. Data up to the event will be analyzed.
There will be no assumptions made for missing data. Data from last observation will be analysed. A drop-out of 20% is accepted in orthopedic trials.

9.2.4 Sensitivity Analysis

The intercurrent events in this trial are progression of osteoarthrosis up to TKA, lost to follow-up, premature death and change to the other treatment group. Progression of osteoarthrosis up to TKA will be defined as procedure failure. Lost to follow-up and premature death can be unrelated to knee problems. Both will be defined as lost to follow up. Lost to follow-up will reduce the power of the result. A drop-out of 20 % is acceptable and will not bias the result.

9.2.5 Supplementary Analysis

Age, sex, and smoking may be subgroups. If there are enough patients for subgroups they will be analyzed.

9.3 Analysis Supporting Secondary Objective(s)

Secondary objectives are:
Safety of the patient, efficacy of the procedure, MRI image description and patient satisfaction.
Patient safety will be analyzing the number of AE, SAE and SUSARs and will be compared for both groups. The numbers obtained will be compared in a Chi-Square test. SUSARs will only occur, if any, in the operated group and thus cannot be compared to any other value. For categorial variables. Efficacy of the procedure will be analyzed by counting the number of failed procedures in the operated group. Because this value will only be determined in the operated group, there is no statistical analysis. The efficacy of the procedure must be over 80%. If the failed procedures are higher than 20 % the benefit-risk balance will be re-evaluated. The MRI signal will be evaluated after a modified scheme of Genovese [32]. The size of the meniscus and the amount of extrusion of the meniscus will be measured and recorded in both groups. The obtained numbers will be compared to the other group at the same time point and to the value before surgery/at the beginning of the trial. This will be performed with an unpaired t-Test if the values are normally distributed or with the Mann-Whitney-U-test for not normally distributed values. Patient satisfaction is a categorial value and will be only evaluated in the operated group. The number of patients who are very pleased, pleased, not pleased, very unsatisfied will be described by means of frequency tables and plots.
Intercurrent event are: progression of osteoarthrosis up to TKA, lost to follow-up, premature death, the patient wishes to change to the operated group after a certain time. If these events happen, the data will be available until the event. Last date recorded will be analyzed. Progression of osteoarthrosis up to TKA will be recorded as fail and will be reported as this. Patients changing to the operated group will be analyzed up to the date of change in the non-operated group. Missing data will not be estimated. A dop-out rate (lost to follow-up, premature death) of 20% is expected and accepted.

9.4 Analysis of Exploratory Objective(s)

Exploratory Estimand (Variable): Progression of osteoarthrosis up to TKA.
The number of patients with progressing osteoarthrosis up to TKA will be represented in a Kaplan-Meier-survival curve for both groups. The equality of the curves will be assessed using logrank tests.

9.5 Safety Analyses

Patient safety will be analyzed by recording AE, SAE and SUSARs. The number of these events will be recorded and compared for both groups. SUSARs will only occur, if any, in the operated group. The frequencies obtained will be displayed in bar plots and tables with group comparisons based on Fisher´s exact test. Safety is a secondary outcome and is described in detail in 9.3.

9.6 Other Analyses

The KOOS score has sub-scores: symptoms, pain, activity in daily live, sport and leisure, and quality of live. This sub-scores will be analyzed in detail for the 2 groups. There will be no adjusted analysis.

9.7 Interim Analyses

Interim analysis will be performed 2 years after surgery/start of the trial. After knee surgery, the usual follow up is 2 years. Because long term results are important for the efficacy of the procedure, evaluations will be performed also after 5 years. The analysis will be performed by the investigator. The statistical methods used are described under 9.2 and 9.3. The outcome data will be seen only by the investigator while the trial is ongoing. The 2-years result will be published in an international orthopedic journal. There will be no group sequential test and no spending function. The number of patients is fixed at 30 in the operated group and at 10 in the non-operated group. There will be no enrollment until an event occurs. There will be no trial adaptation or changes to the eligibility criteria.
Stopping criteria are: If AE, SAE and SUSARs change the benefit-risk balance, there will be a new benefit-risk balance evaluation and after this evaluation it will be decided if the trial will be stopped. The investigator expects a maximal 20% failure rate of the procedure. If the failure rate is higher a new benefit-risk balance evaluation must be performed and after the evaluation it must be decided if the trial continues. If the safety of the patients is not any more given, the trial should be stopped.
The investigator also has the right to stop the trial. This could be because of the closure of the site. See 10.5 for details.

9.8 Sample Size Determination

The unpaired t-Test will be used for normally distributed PROMs. Values for the primary outcome are expected to be about 55/84 for the IKDC score and 46/86 for the KOOS pre/postsurgery, respectively. For this calculation, the program G-power was used. A sample size of 9 in the operated group and 3 in the non-operated group would be sufficient to reach a power of 0.982. When we include 10 non-operated patients and 30 operated patients the effect size is 2.0, $\alpha = 0.00655$ and the power is than 0.993. If we have a 20% lost to follow-up, the numbers of patients will be 8/24 and $\alpha = 0{,}014$ and the power will be 0.985. The number of 30/10 is sufficient to reach a power of >0.8.

9.9 Protocol Deviations

There will be no protocol deviations, because the surgery will be performed after a standardized procedure for each patient at the beginning of the trial and the follow-up visits will be performed after a predefined standardized protocol. There are no treatments planned after surgery. The tight follow-up plan will secure patient safety.

10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

The Investigator is also the sponsor. He is responsible for compliance with the below laws and regulations.
The clinical trial will be conducted in compliance with the protocol, with the regulation and with the principles of good clinical practice according to Annex I section D 17 (a) CTR 536/2014, the declaration of Helsinki, the Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines, ICH Good Clinical Practice (GCP) Guidelines (the investigator holds the ICH-GCP-certificate). Additionally the German Bundesdatenschutzgesetz (BDSG) and the General Data protection Regulation (regulation (EU)2016/679), GDPR) will be followed.
The study will only start after a positive ethic vote is obtained.
The benefit-risk balance is in focus of the trial and will be evaluated when safety issues occur. The efficacy of the procedure is also in focus and only when the efficacy is over 80% the ethical balance is given.

10.2 Committees

This is an investigator-initiated trial (Investigator=Sponsor). There will be no committee be involved in the trial.

10.3 Informed Consent Process

The informed consent process starts with the first appointment. When patients are referred for partial meniscal replacement, they will be informed about the clinical trial. If the patient qualifies for participation in the study based on the inclusion and exclusion criteria, the investigator will explain the treatment procedure for partial meniscus replacement with Spongioflex® and the planned investigator-initiated trial (planned visits, data protection, etc.). Patients also receive an information sheet explaining the study and the surgical procedure, the advantages and disadvantages, the risks, and the follow-up treatment. The information sheet also provides information about the planned investigator-initiated study (planned visits, data protection, etc.). After a sufficient reflection period, the patient must sign the declaration of consent to participate in the investigator-initiated study and the data protection declaration. Without these written consents, the patient cannot be included in the investigator-initiated trial. After the signatures have been obtained, the patient is included in the investigator-initiated trial. The patient decides whether to undergo surgery. The operation is performed in accordance with standard clinical practice and the usual risk information for the surgical procedure. This is done using the standard information sheet used in the respective hospital. In this, patients are usually informed about the procedure, the treatment alternatives, the risks, and the follow-up treatment.
Enrollment in the trial does NOT occur during an emergency in which the participant or their legally authorised representative is not able or available to give consent.

Rescreening
Rescreening can be performed when the patient did not meet the inclusion criteria (e.g. age) in the first attempt. If any exclusion criteria are not any more valid (e.g. BMI) rescreening can be performed. The screening will be performed even, when the patient does not agree to participate in the study, because than the patient will be treated/or not, but the data will not be collected for the study. The informed consent will be obtained after enrollment, when inclusion criteria are met and no exclusion criteria are met. Screen failure will be left in because the study model is full analysis set. When re-screening is performed informed consent is mandatory for participation in the study.
There will be no collection of (biological) samples in the study.

10.4 Data Protection

All collected and stored data of the study participants are treated confidentially and are subject to medical confidentiality. The patient's right to respect his/her privacy and the protection of data concerning him/her is guaranteed in accordance with the General Data Protection Regulation (DSGVO) of 25.5.2018. The personal data are only accessible to the performing physician in the study center, who has included the patient, or to employees commissioned by him. The personal data will only be processed in pseudonymous form. For this purpose, the study center creates a pseudonymization list, which is only known to the authorized employees of the study center. The data are pseudonymized in ascending order for scientific analysis, so that third parties (biometricians) cannot establish a personal reference. In this study, the investigator and the sponsor are the same person. Therefore, no transfer of data between the investigator and the sponsor is necessary. Furthermore, it is intended that the investigator performs the analysis himself. If a biometrician (statistician) must be consulted for the evaluation, he will only receive the pseudonymized CRF, from which no conclusions can be drawn about the patient or the clinic in which the patient was treated. The pseudonymization will be performed by attributing numbers and special characters. Initials and birth dates are not used for pseudonymization and are omitted. For the patient, there is a right of access and objection at any time with the possibility to delete all collected data. Patients can withdraw their consent to participate in the study and to data collection at any time without giving reasons. This does not change medical treatment. The study is therefore a minimal interventional study, as the treatment is conducted in the same way with and without study participation. The only difference is that the data are only stored in the patient chart if the patient does not participate in the study and not transferred to the CRF after pseudonymization. If the patient's consent is withdrawn, the responsible bodies will immediately check the extent to which the stored data are still required. Data that are no longer required will be deleted immediately, unless statutory documentation and reporting obligations prevent this. However, the data processing conducted up to the point of withdrawal remains lawful.
Safety of Data and patients is monitored by a CRA (clinical monitor).
In case of a data security breach the patient will be informed about the breach without undue delay and at the latest within 7 days. Additionally, the data security breach will be reported to the EU portal and EU database (via the CTIS) without undue delay and at the latest within 7 days. The template provided at the CTIS should be filled in and all information which are described under 5 and appendix IIIb of the Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol (EMA/698382/2021) from the 30th of June 2023.

10.5 Early Site Closure or Trial Termination

Site closure:
The Investigator and the Sponsor are the same person. The investigator has the right to close the site. This could be for physical or financial reasons. The ethic committee will be informed and a prompt notification of the patients will be performed. The treatment is the surgery and is terminated when the site is closed. The remaining follow-up’s will be performed by an orthopedic surgeon, who is familiar with the procedure and the follow-up.

Termination or suspension:
The investigator-initiated trial may only be terminated prematurely for ethically relevant, i.e., medical/ scientific reasons.
Premature exclusion of a patient from the study:

- If, during the waiting period for the Spongioflex® graft, changes in the patient's state of health occur that constitute a contraindication for partial meniscal implantation (e.g., infection of the knee joint, tibial

plateau fracture), the physician conducting the study must withdraw the patient from the investigator-initiated trial if this appears reasonable and necessary for medical reasons.

Premature termination of the entire study: Reasons for premature termination of the investigator-initiated trial include:

- If the identifiable risks outweigh the expected benefits.
- If an unreasonable risk to patients is apparent
- If unexpected serious adverse events (SAE); Suspected Adverse Drug Reaction (SADR) occur that are causally related to the insertion of the meniscal implant they will be reported to the EudraVigilance database. A new benefit/risk balance evaluation is performed and after the analysis it is decided if the study will be continued. Patients will be followed up until the SAE or SADR is solved, if necessary, in the hospital, otherwise as outpatient.
- IF SUSARs are reported, a new benefit/risk balance evaluation is performed and after the analysis it is decided if the study will be continued.

If the investigator-initiated trial is terminated or suspended prematurely, the study director will inform the regulatory authority(ies) of the termination or suspension and provide a statement to that effect. The Ethic Committee will be promptly notified and provided with a detailed written explanation for the study director's termination or suspension of the investigator-initiated trial, as specified in the applicable regulatory requirements. If the investigator-initiated trial is terminated or suspended prematurely for any reason, study participants will be notified immediately.

- In the event of premature termination or suspension of the investigator-initiated trial, further follow-up of patients will continue according to standard clinical practice

Patients can stop the participation of the study at any time, without giving the reason for it.

11 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

Quality tolerance limits are defined in the inclusion/exclusion criteria. The main criteria which may lead to exclusion of the patient from the trial are age (must be over 18 years and under 60 years) and BMI (must be <30 kg/m²). The investigator expects a 20% drop in total. If the drop-out will be higher, this could significantly impact the study results. Protocol deviations and violations will not occur, because the surgery is performed after a standardized procedure. The patient does not have any impact on this procedure.
The percentage of withdrawal will be small, because the burden of the trial is very low (filling the 3 questionnaires at the follow-up-visit). The investigator predicts a maximum of 5 % withdrawal, which is included in the 20% mentioned above.
Incomplete data will occur due to lost to follow-up, withdrawal or due to progression of osteoarthrosis up to TKA. Progression of osteoarthritis is a very slow process; thus a 2.5% possibility would be defined by the investigator for incomplete data related to progression of osteoarthritis up to TK.
AE and SAE occur at any time and may be not related to the IMP used. SAE not related to the investigational product do not impact study results. SADR/SUSAR's do impact study results. Because human allogeneic cortical bone (in any supply form) was transplanted in different forms several thousand-fold, the manufacturer (DIZG gGmbH, Berlin, Germany) did not receive any information about and SADR or SUSAR up to now.
The IMP is not a pharmacological drug and the administration is not over the trial period. The IMP will be implanted during surgery and remains in the body. It has no systemic effect and it is not a medical device.
Patient follow-up will be the same for patients included in the trial or not, thus the lost to follow-up will be below 10 %, because the follow-up-visits are only a minimal burden.
For ethical reasons, there is no randomization in the trial. The patient decides, if he will be operated, or not. Even if the patient will decide not to be operated in the first round, they have the possibility to change to the surgery group at any time. Thus, there is no pressure on the patient and there is no incorrectly randomized patient.
All this Quality tolerance limits are monitored during the trial via a clinical monitor (CRA).

11.2 Data Quality Assurance

This is an investigator-initiated trial. The private practice consists of an orthopedic surgeon and a part time medical assistant. The investigator is also the sponsor of the trial and is also responsible for quality assurance. A clinical monitor will verify the quality of the data.

11.3 Source Data

Definition of Source Data:
Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.
The source data in this clinical trial are the electronic patient charts. They are attributable, legible, contemporaneous, original, and accurate and meet regulatory requirements. For this trial, this includes the MRI, the PROM's, and the operative report (for the operated group). Data of patients who take part in the study will be transferred to the CRF in pseudonymized form. No date of birth or initials will be transferred. The pseudonymization list and the CRF will be only available to the orthopedic surgeon and the access is controlled and the hardcopy of the pseudonymization list and the CRF is saved in a safe. The investigator

permits trial-related monitoring, audits, IRB/IEC review and regulatory inspections providing direct access to source data/documents. The clinical monitor will regularly verify CRF-Data relative to source data. Safety of participants is protected and the conduct is in accordance with GCP.

12 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

12.1 Further Details and Clarifications on the AE Definition

There are no regional AE requirements. An adverse event log is filled to follow the adverse event until it is solved.
A trial related adverse event is redness, haematoma, swelling, infection of the operated site and pain of the treated knee. This will be recorded in the electronic patient chart and in the CRF.
Progression of osteoarthritis up to TKA does not meet AE definition; it is the normal progression of the disease and will be expected to be more observed in the non-operated group.
The IMP of this clinical trial is human cancellous bone, there is no dose, there are only dimensions of the transplant. Thus, there is no overdose.
Lack of efficacy of the procedure is provided when more than 20% of the procedures fail.

12.2 Further Details and Clarifications on the SAE Definition

SAEs must be reported immediately to the IRB/IEC except for those SAEs that the protocol identifies as not needing immediate reporting. Additionally SAEs related to the IMP are reported to the EudraVigilance Data base and via the CTIS webpage.
A trial related SAE is an allergic reaction against the IMP.
Progression of osteoarthritis up to TKA does not meet SAE definition; it is the normal progression of the disease and will be expected to be more observed in the non-operated group.
On the Webpage of the PEI there is a document (https://www.pei.de/DE/arzneimittelsicherheit/gewebevigilanz/meldeformulare/meldeformulare-node.html, Form G1a) to be filled in for :" Meldung des Verdachts einer schwerwiegenden unerwünschten Empfängerreaktion im Zusammenhang mit der Übertragung von Gewebe, Gewebezubereitungen oder Stammzellen gemäß § 63i AMG" this form would be filled and send to the PEI.

12.3 Severity

Definition Severity:
Severity is the intensity of a specific event. The event itself can be of minor medical significance.

- Grade 1: Mild — transient or mild discomfort (< 48 hours); no medical intervention/ therapy required.
- Grade 2: Moderate — mild to moderate limitation in activity — some assistance may be needed; no or minimal medical intervention/ therapy required.
- Grade 3: Severe — marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.
- Grade 4: Life-Threatening — extreme limitation in activity; significant assistance required; significant medical intervention/therapy required, hospitalization, or hospice care probable.
- Grade 5: Death.

12.4 Causality

Definition Causality: Causality is an influence by which one event, process, state, or object (a cause) contributes to the production of another event, process, state, or object (an effect) where the cause is partly responsible for the effect, and the effect is partly dependent on the cause. It is an evaluation of the likelihood that a particular treatment is the cause of an observed adverse event (AE).

Causality Categories:

- definitely related
- probable
- possible
- unlikely
- unclassified/unassessable
- Causality ruled out/unrelated

Procedure for assessing methodology: (WHO Methodology)

- definitely related: good timing, no other cause, withdrawal response plausible, rechallenge, “definite”
- probable: good timing, other cause unlikely, withdrawal
- possible: good timing, other cause possible
- unlikely: poor timing, other cause more likely
- unassessable: insufficient or contradictory information

13 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

13.1 Contraception and Pregnancy Testing

13.1.1 Definitions Related to Childbearing Potential

Participants of childbearing potential are females which can become pregnant. These patients can take part in the study, but when they decide for the operated group, they must make a pregnancy test before surgery. After surgery they can become pregnant. This does not influence study results.
All patients with non-childbearing potentials are male or female after menopause. They can take part in the study without a pregnancy test.

13.1.2 Contraception

Contraception does not have to be taken. A pregnancy test before surgery is sufficient for childbearing potential patients who wish to be operated.

13.1.3 Pregnancy Testing

Pregnancy testing is only required for patients who will be operated and have childbearing potential.

13.2 Clinical Laboratory Tests

Trial specific laboratory testing is not necessary and not planned. Only the normal laboratory testing will be performed for patients who will be operated.

13.3 Country/Region-Specific Differences

The trial will be conducted only in Germany, there are no country/region specific differences to the above explained rules.

13.4 Prior Protocol Amendments

This protocol has not been amended

14 APPENDIX: GLOSSARY OF TERMS

Abbreviations

AE;	Adverse event
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CMI:	Collagen Meniscus Implant
FSA-Kodex:	freiwillige Selbstkontrolle der Arzneimittelindustrie
ICRS	International Cartilage Repair Society
IKDC:	International Knee Documentation Committee Score
IMP:	investigational medicinal product
IRB/IEC	Institutional Review Board/Institutional Ethic Committee
KOOS:	Knee injury and Osteoarthritis Outcome Score
PEI	Paul Ehrlich Institut
PROM:	Patient Recorded Outcome Measures
SADR:	Serious adverse Drug reaction
SAE:	Serious adverse event
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TKA:	total knee arthroplasty
VAS Pain Score:	Visual analogue pain scale

15 APPENDIX: REFERENCES

1. Outerbridge, R.E. The etiology of chondromalacia patellae. *The Journal of bone and joint surgery. British volume* **1961**, *43-b*, 752-757, doi:10.1302/0301-620x.43b4.752.
2. Ahmed, A.M.; Burke, D.L. In-vitro measurement of static pressure distribution in synovial joints--Part I: Tibial surface of the knee. *J Biomech Eng* **1983**, *105*, 216-225, doi:10.1115/1.3138409.
3. Petty, C.A.; Lubowitz, J.H. Does arthroscopic partial meniscectomy result in knee osteoarthritis? A systematic review with a minimum of 8 years' follow-up. *Arthroscopy* **2011**, *27*, 419-424, doi:10.1016/j.arthro.2010.08.016.
4. Fairbank, T.J. Knee joint changes after meniscectomy. *The Journal of bone and joint surgery. British volume* **1948**, *30b*, 664-670.
5. Andersson-Molina, H.; Karlsson, H.; Rockborn, P. Arthroscopic partial and total meniscectomy: A long-term follow-up study with matched controls. *Arthroscopy* **2002**, *18*, 183-189, doi:10.1053/jars.2002.30435.
6. Hoser, C.; Fink, C.; Brown, C.; Reichkendler, M.; Hackl, W.; Bartlett, J. Long-term results of arthroscopic partial lateral meniscectomy in knees without associated damage. *The Journal of bone and joint surgery. British volume* **2001**, *83*, 513-516, doi:10.1302/0301-620x.83b4.11364.
7. Papalia, R.; Franceschi, F.; Diaz Balzani, L.; D'Adamio, S.; Maffulli, N.; Denaro, V. Scaffolds for partial meniscal replacement: an updated systematic review. *Br Med Bull* **2013**, *107*, 19-40, doi:10.1093/bmb/ldt007.
8. Barrett, G.R.; Field, M.H.; Treacy, S.H.; Ruff, C.G. Clinical results of meniscus repair in patients 40 years and older. *Arthroscopy* **1998**, *14*, 824-829, doi:10.1016/s0749-8063(98)70018-0.
9. Cannon, W.D., Jr.; Vittori, J.M. The incidence of healing in arthroscopic meniscal repairs in anterior cruciate ligament-reconstructed knees versus stable knees. *Am J Sports Med* **1992**, *20*, 176-181, doi:10.1177/036354659202000214.
10. Williams, R.J., 3rd; Warner, K.K.; Petrigliano, F.A.; Potter, H.G.; Hatch, J.; Cordasco, F.A. MRI evaluation of isolated arthroscopic partial meniscectomy patients at a minimum five-year follow-up. *Hss j* **2007**, *3*, 35-43, doi:10.1007/s11420-006-9031-2.
11. Englund, M.; Guermazi, A.; Roemer, F.W.; Aliabadi, P.; Yang, M.; Lewis, C.E.; Torner, J.; Nevitt, M.C.; Sack, B.; Felson, D.T. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The Multicenter Osteoarthritis Study. *Arthritis Rheum* **2009**, *60*, 831-839, doi:10.1002/art.24383.
12. Englund, M.; Lohmander, L.S. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. *Arthritis Rheum* **2004**, *50*, 2811-2819, doi:10.1002/art.20489.
13. Rodkey, W.G.; DeHaven, K.E.; Montgomery, W.H., 3rd; Baker, C.L., Jr.; Beck, C.L., Jr.; Hormel, S.E.; Steadman, J.R.; Cole, B.J.; Briggs, K.K. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. *J Bone Joint Surg Am* **2008**, *90*, 1413-1426, doi:10.2106/jbjs.G.00656.
14. Rodkey, W.G.; Steadman, J.R.; Li, S.T. A clinical study of collagen meniscus implants to restore the injured meniscus. *Clin Orthop Relat Res* **1999**, S281-292, doi:10.1097/00003086-199910001-00027.
15. Schenk, L.; Bethge, L.; Hirschmann, A.; Berbig, R.; Lüthi, U.; Arnold, M.P.; Hirschmann, M.T. Ongoing MRI remodeling 3-7 years after collagen meniscus implantation in stable knees. *Knee Surg Sports Traumatol Arthrosc* **2020**, *28*, 1099-1104, doi:10.1007/s00167-019-05714-w.
16. Dabaghi, M.; Eras, V.; Kaltenhaeuser, D.; Ahmed, N.; Wildemann, B. Allografts for partial meniscus repair: an in vitro and ex vivo meniscus culture study. *Front Bioeng Biotechnol* **2023**, *11*, 1268176, doi:10.3389/fbioe.2023.1268176.
17. Scotti, C.; Hirschmann, M.T.; Antinolfi, P.; Martin, I.; Peretti, G.M. Meniscus repair and

regeneration: review on current methods and research potential. *Eur Cell Mater* **2013**, *26*, 150-170, doi:10.22203/ecm.v026a11.
18. Pereira, H.; Fatih Cengiz, I.; Gomes, S.; Espregueira-Mendes, J.; Ripoll, P.L.; Monllau, J.C.; Reis, R.L.; Oliveira, J.M. Meniscal allograft transplants and new scaffolding techniques. *EFORT Open Rev* **2019**, *4*, 279-295, doi:10.1302/2058-5241.4.180103.
19. Dickerson, D.A.; Misk, T.N.; Van Sickle, D.C.; Breur, G.J.; Nauman, E.A. In vitro and in vivo evaluation of orthopedic interface repair using a tissue scaffold with a continuous hard tissue-soft tissue transition. *J Orthop Surg Res* **2013**, *8*, 18, doi:10.1186/1749-799x-8-18.
20. Credille, K.T.; Wang, Z.R.C.; Horner, N.S.; Regan, D.P.; Gadomski, B.C.; Easley, J.T.; Garrigues, G.E.; Yanke, A.B. Biphasic Interpositional Allograft for Rotator Cuff Repair Augmentation Is Safe in an Ovine Model. *Arthroscopy* **2023**, *39*, 1983-1997, doi:10.1016/j.arthro.2023.03.018.
21. Minkus, M.; Akgün, D.; Thiele, K.; Karpinski, K.; Moroder, P. Bankart-Plus zur Behandlung von Patienten mit anteriorer Schulterinstabilität und kleinen bis moderaten Glenoiddefekten. *Obere Extremität* **2022**, *17*, 243-249, doi:10.1007/s11678-022-00710-y.
22. Smith, M.J.; Pfeiffer, F.M.; Cook, C.R.; Kuroki, K.; Cook, J.L. Rotator cuff healing using demineralized cancellous bone matrix sponge interposition compared to standard repair in a preclinical canine model. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* **2018**, *36*, 906-912, doi:10.1002/jor.23680.
23. Sundar, S.; Pendegrass, C.J.; Blunn, G.W. Tendon bone healing can be enhanced by demineralized bone matrix: a functional and histological study. *J Biomed Mater Res B Appl Biomater* **2009**, *88*, 115-122, doi:10.1002/jbm.b.31157.
24. Hui, P.W.; Leung, P.C.; Sher, A. Fluid conductance of cancellous bone graft as a predictor for graft-host interface healing. *Journal of Biomechanics* **1996**, *29*, 123-132, doi:10.1016/0021-9290(95)00010-0.
25. Wildemann, B.; Kadow-Romacker, A.; Haas, N.P.; Schmidmaier, G. Quantification of various growth factors in different demineralized bone matrix preparations. *J Biomed Mater Res A* **2007**, *81*, 437-442, doi:10.1002/jbm.a.31085.
26. Wildemann, B.; Kadow-Romacker, A.; Pruss, A.; Haas, N.P.; Schmidmaier, G. Quantification of growth factors in allogenic bone grafts extracted with three different methods. *Cell Tissue Bank* **2007**, *8*, 107-114, doi:10.1007/s10561-006-9021-0.
27. Monllau, J.C.; Gelber, P.E.; Abat, F.; Pelfort, X.; Abad, R.; Hinarejos, P.; Tey, M. Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. *Arthroscopy* **2011**, *27*, 933-943, doi:10.1016/j.arthro.2011.02.018.
28. Zaffagnini, S.; Marcheggiani Muccioli, G.M.; Lopomo, N.; Bruni, D.; Giordano, G.; Ravazzolo, G.; Molinari, M.; Marcacci, M. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: a minimum 10-year follow-up study. *Am J Sports Med* **2011**, *39*, 977-985, doi:10.1177/0363546510391179.
29. Stone, K.R.; Rodkey, W.G.; Webber, R.; McKinney, L.; Steadman, J.R. Meniscal regeneration with copolymeric collagen scaffolds. In vitro and in vivo studies evaluated clinically, histologically, and biochemically. *Am J Sports Med* **1992**, *20*, 104-111, doi:10.1177/036354659202000202.
30. Bulgheroni, P.; Murena, L.; Ratti, C.; Bulgheroni, E.; Ronga, M.; Cherubino, P. Follow-up of collagen meniscus implant patients: clinical, radiological, and magnetic resonance imaging results at 5 years. *The Knee* **2010**, *17*, 224-229, doi:10.1016/j.knee.2009.08.011.
31. Behrendt, S. MRI follow up of bilateral partial meniscal substitution with a demineralized bone block. A case report. *Radiol Case Rep* **2023**, *18*, 21-26, doi:10.1016/j.radcr.2022.09.091.
32. Genovese, E.; Angeretti, M.G.; Ronga, M.; Leonardi, A.; Novario, R.; Callegari, L.; Fugazzola, C. Follow-up of collagen meniscus implants by MRI. *Radiol Med* **2007**, *112*, 1036-1048, doi:10.1007/s11547-007-0204-y.

33. Kellgren, J.H.; Lawrence, J.S. Radiological assessment of rheumatoid arthritis. *Ann Rheum Dis* **1957**, *16*, 485-493, doi:10.1136/ard.16.4.485.