Der Balgrist

Clinical Study Protocol

Randomized Controlled Trial for the Use of an Osteoconductive Scaffold in ACL-Reconstruction

Study Type:	Clinical trial with Investigational Medical Device (IMD)
Study Categorization:	Clinical Trial with IMD Category A
Study Registration:	SNCTP and clinical.trials.gov
Sponsor-Investigator and Principal Investigator:	PD Dr. med. Sandro F. Fucentese
Investigational Medical Device:	SmartBone (IBI S. A.)
Investigation plan Version and Date:	V2.0 / 06.06.2017

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SIGNATURE PAGE

Study number

Study Title Randomized Controlled Trial for the Use of an Osteoconductive Scaffold in ACL-Reconstruction

Sponsor-Investigator (Principal Investigator):

The Sponsor-Investigator has approved the investigation plan version 2.0 of 06.06.2017, and confirms hereby to conduct the study according to the investigation plan, current version of the World Medical Association Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

PD Dr. med. Sandro F. Fucentese

Place/Date	Signature

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STUDY SYNOPSIS

Sponsor-Investigator	PD Dr. med. Sandro F. Fucentese
Study Title:	Randomized Controlled Trial for the Use of an Osteoconductive Scaffold in ACL-Reconstruction
Short Title / Study ID:	ACLROCS
Protocol Version and Date:	V2.0, 6 June 2017
Trial registration:	• Swiss Federal National Clinical Trials Portal SNCTP • International trial registry ClinicalTrials.gov
Study category and Rationale	Category A, as the device under study bears a conformity marking and is to be used in accordance with the instructions.
Clinical Phase:	Post-market efficacy trial using an implantable CE-marked medical device
Background and Rationale:	Reconstruction of the anterior cruciate ligament (ACL) using autograft tissue is currently recommended as the standard of care following an ACL tear or rupture, with the bone-tendon-bone (BTB) graft and hamstring tendon graft the most common. Although a BTB autograft is widely recognized to offer high mechanical performance and rapid graft healing, these advantages come at the cost of a longer surgery time and higher risk of severe patient discomfort at the graft harvest site. Use of a hamstring tendon autograft is less painful, but is generally slower to heal with higher risk of mechanical graft failure due to poor bone ingrowth. The aim of the current study is to augment graft-to-bone incorporation by use of an osteoconductive scaffold enlaced into the hamstring tendon autograft. This bovine derived composite bone substitute is inserted into the articular aperture of the femoral bone tunnel and should provide an osteoconductive / osteoinductive environment at a biomimetic attachment site leading to improved secondary graft-fixation and a reduced incidence of tunnel widening.
Objective(s):	Primary objective of the study is to evaluate efficacy of the surgical technique for ACL reconstruction using an osteoconductive scaffold, enlaced into the hamstring tendon autograft, compared to the traditional technique. Secondary objectives aim to assess the clinical outcome of the interventional treatment including patient subjective knee function and objective measures of knee stability.
Outcome(s):	The primary efficacy outcome of this study will be the CT based relative change of the femoral bone tunnel volume. Secondary outcome measures for patient subjective knee function include International Knee Documentation Committee Subjective Knee Evaluation Form, Lysholm Knee Scoring Scale and Tegner Activity Scale. Knee stability will be assessed using the KT-1000 Arthrometer Test, the Lachman Test and the Pivot Shift Test. Safety will be evaluated by the occurrence, frequency and severity of intra- and postoperative complications.
Study design:	Randomized patient-blinded two-group parallel comparison trial using an active comparator.

Inclusion / Exclusion criteria:	Inclusion Criteria: • 18 to 60 years of age. • Males and females. • Acute unilateral complete tear of the ACL that occurred within 18 weeks before planned surgery and requires reconstruction of the ACL. • Informed consent as documented by signature Exclusion Criteria: • Prior ACL reconstruction or other surgical procedure on the affected knee. • Prior fracture of the affected leg. • Multi-ligament reconstruction. • Previous or current ACL injury on contra-lateral leg. • Medical condition or comorbidity that would interfere with study participation. • The patient is mentally compromised. • Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant. • Other clinically significant concomitant disease states (e.g. renal failure, hepatic dysfunction, cardiovascular disease, etc.). More in- and exclusion criteria on page 28

Measurements and procedures:	Screening (Visit 1): • Patient information Surgery (Visit 2): • Informed consent completed and signed • Check of inclusion and exclusion criteria • Medical/surgical history • Pregnancy test • Randomization • ACL-reconstruction (interventional/control) according to assigned group • Recording of AE's (if any) • CT scanning • Plain radiography • Clinical examination • Patient subjective knee function • Knee stability assessment • Tegner activity scale • Patient demographics Follow-up 1 (Visit 3) • Plain radiography/Pregnancy Test • Patient subjective knee function • Tegner activity scale • Knee stability assessment • Clinical examination • Recording of AE's (if any) Follow-up 2 + 3 (Visit 4 + 5): • CT scanning/Pregnancy test • Plain radiography • Patient subjective knee function • Tegner activity scale • Knee stability assessment • Clinical examination • Recording of AE's (if any) Follow-up 4 (Visit 6) • Plain radiography/Pregnancy test • Patient subjective knee function • Tegner activity scale • Knee stability assessment • Clinical examination • Recording of AE's (if any) Final Follow-up (Visit 7): • Patient subjective knee function • Tegner activity scale • Knee stability assessment • Clinical examination • Recording of AE's (if any)

Study Product / Intervention:	The device under study is a composite bone substitute composed of a natural mineral matrix of bovine origin, reinforced with biodegradable synthetic polymers and natural collagen derivatives of bovine origin. Before graft insertion this osteoconductive scaffold is enlaced into the folded hamstring tendon-graft, tied off using surgical suture and connected to the cortical suspension device. During surgery the graft is inserted through the medial portal and pulled into the femoral socket so that the scaffold is positioned at the articular aperture of the femoral bone tunnel.
Control Intervention:	ACL-reconstruction using hamstring autograft with hybrid fixation in accordance with standard of care.
Number of Participants with Rationale:	A total of 56 patients are required to detect a minimal clinically important difference in relative change of bone tunnel volume after a 2-year follow-up of 20% given an assumed standard deviation of 25.2% with a power of 0.8 and an α-error of 0.05 and accounting for a drop-out rate of 10% for this equally sized two-group parallel design.
Study Duration:	Expected duration for patient acquisition: 22 months Expected time from first patient acquisition to the end of follow-up of the last patient: 82 months Statistic and Abstract: ca. 6 months
Study Schedule:	First-Patient-In: 07/2017 Last-Patient-Out: 05/2024 Statistics/Abstract: 12/2024
Investigator(s):	PD Dr. med. Sandro F. Fucentese University Hospital Balgrist
Study Centre(s):	University Hospital Balgrist
Statistical Considerations:	Intention-To-Treat analysis Independent t-test on the primary efficacy outcome comparing the two groups with a significance level of 0.05, 2-sided.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

STUDY SUMMARY IN LOCAL LANGUAGE

Das vordere Kreuzband verläuft im Kniegelenk von der Oberschenkelrolle zum Schienbeindach und stabilisiert zusammen mit dem hinteren Kreuzband das Kniegelenk. Durch diese Führung werden andere Strukturen des Kniegelenks wie Menisken und Knorpel gegen eine Zerstörung geschützt. Rupturen des Kreuzbandes treten häufig in Sportarten die schnelle Richtungswechsel beinhalten (z.B. Fussball, Basketball) und im Bereich Ski Alpin auf. Zur Rekonstruktion des vorderen Kreuzbandes wird meist körpereigenes Material als Transplantat verwendet. Hierzu wird das mittlere Drittel des Kniescheibenbands (Patellarsehne) mit je einem kleinen Knochenblock aus der Kniescheibe und dem Unterschenkel entnommen. Alternativ können auch Beugesehnen an der Innenseite des Kniegelenks (Semitendinosus- oder Gracilissehne) als Transplantat verwendet werden. Das Transplantat wird mittels Kniegelenksspiegelung (arthroskopisch) in Bohrkanälen im Oberschenkel respektive im Unterschenkel mit Hilfe von Schrauben oder Stiften fixiert. Die Verwendung des Kniescheibenbands bietet hierbei den Vorteil eines beschleunigten Einwachsens des Transplantats in den Bohrkanal. Jedoch können an der Entnahmestelle Komplikationen wie Schmerzen und Kniescheibenfrakturen auftreten. Da bei der Verwendung einer Beugesehne kein Knochenblock entnommen wird, ist deren Entnahme unproblematischer, der Heilungsverlauf im Bohrkanal aber oft langwieriger. Das zu testende Medizinprodukt besteht aus einem knochenwachstumsinduzierenden Knochenersatz. Dieser soll das Einwachsen des Beugesehnentransplantats in den Bohrkanal beschleunigen. Der Knochenersatz wird in das Sehnentransplantat eingefädelt und kommt nach dessen Einziehen am gelenksnahen Ende des Bohrkanales im Oberschenkel zu liegen.

Zweck dieser Studie ist es, bei insgesamt 56 Patienten den Heilungsverlauf nach Kreuzbandrekonstruktion mit der zu untersuchenden Technik, mit der herkömmlichen Methode zu vergleichen. Primär untersucht wird das Auftreten von etwaigen Komplikationen sowie die Verknöcherung des Bohrkanals, ermittelt durch radiologische Untersuchungen. Hierzu werden der Heilungsverlauf, sowie die Patientenzufriedenheit und die Kniestabilität über einen Zeitraum von 5 Jahren verfolgt.

ABBREVIATIONS

ACL	Anterior cruciate ligament
AE	Adverse Event
BPTB	Bone patellar tendon bone
BTW	Bone tunnel widening
CA	Competent authorities (Swissmedic)
CEC	Competent Ethics Committee
ClinO	Clinical Trials Ordinance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common terminology criteria for adverse events
eCRF	Electronic Case Report Form
FMEA	Failure Mode and Effects Analysis
H0	Null hypothesis
H1	Alternative hypothesis
HA	Hydroxyapatite
IFU	Instructions for use
IKDC	International Knee Documentation Commitee
IKDC SKEF	IKDC Subjective Knee Evaluation Form
IMD	Investigational Medical Device
ISF	Investigator Site File
ITT	Intention to Treat
LHR	Law on human research
LKSS	Lysholm Knee Scoring Scale
MRI	Magnetic resonance imaging
PI	Principal Investigator
PLDLLA	Poly(l-lactide-co-D,l-lactide)
PLLA	poly-l-lactic acid
SAE	Serious Adverse Event
SDV	Source Data Verification
SN	Study Nurse
SNCTP	Swiss National Clinical Trial Portal
SOP	Standard Operating Procedure
TAS	Tegner Activity Scale
TMF	Trial Master File
WI	Work Instruction
β-TCP	β-Tricalcium phosphate

STUDY SCHEDULE

Study Periods	Screening	Surgery	Follow-up				
Visit	**1**	**2**	**3**	**4**	**5**	**6***	**7***
Time [days/weeks/months /years]	**-3wk (±14d)**	**0**	**42d (±10d)**	**4.5m (±1m)**	**1 y (±2m)**	**2 y (±2m)**	**5 y (±4m)**
Patient Information and Informed Consent	***X****						
Demographics	***X****						
Medical History	x						
In- /Exclusion Criteria	***X****	***X****					
Pregnancy Test		***X****	***X****	***X****	***X****	***X****	
Clinical Examination		x	x	x	x	***X****	***X****
Randomization		***X****					
CT scanning		***X****		***X****	***X****		
Plain Radiography		x	x	x	x	***X****	
Tegner Activity Scale		x	x	x	x	***X****	***X****
IKDC Subjective Knee Evaluation Form		x	x	x	x	***X****	***X****
Lysholm Knee Scoring Scale		x	x	x	x	***X****	***X****
KT-1000 Arthrometer Testing		x	x	x	x	***X****	***X****
Lachmann Test		x	x	x	x	***X****	***X****
Pivot Shift Test		x	x	x	x	***X****	***X****
Primary variables		x	x	x	x		
Secondary variables		x	x	x	x	***X****	***X****
Adverse Events		***X****	***X****	***X****	***X****	***X****	***X****

X* / * Study specific

1 STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor - Principal investigator

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2 ETHICAL AND REGULATORY ASPECTS

Before this study will be conducted, the investigation plan, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) in agreement with local legal requirements, for formal approval. Any amendment to the investigation plan must as well be approved.

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study Registration

The study will be registered in the Swiss Federal National Clinical Trials Portal SNCTP and in the international trial registry ClinicalTrials.gov.

2.2 Categorization of Study

Category A study with medical device. The device under study bears a conformity marking and is used in accordance with the instructions.

2.3 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for the study site in the clinical trial. The reporting duties and allowed time frame are respected. No substantial changes are made to the investigation plan without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter Investigation Plan Amendments.

2.4 Competent authorities (CA)

CA (swissmedic) approval is only necessary for category B and C studies. Category A studies do not require a CA approval. The CA is entitled to carry out inspections of all clinical trials.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. CEC will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of Interest

This study will mainly be financed by ZuriMED Technologies AG.

PD Dr. Sandro F. Fucentese is co-inventor of a patent which is licensed to ZuriMED Technologies AG.

Prof. Jess G. Snedeker is co-inventor of a patent which is licensed to ZuriMED Technologies AG. Also he is a shareholder of named company.

Elias Bachmann is co-inventor of a patent which is licensed to ZuriMED Technologies AG. Also he is a shareholder and partially employed by named company.

Tobias Götschi is partially employed by ZuriMED Technologies AG.

2.7 Patient Information and Informed Consent

The investigator will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.

The participant will be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for this study will be provided a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study.

The participant information sheet and the consent form will be submitted with the investigation plan for review and approval for the study by the CEC. The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant Privacy and Confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant’s personal physician or to other appropriate medical personnel responsible for the participant’s welfare, if the patient has given his/her written consent to do so.

For data verification purposes, authorized representatives of the Sponsor-Investigator and an ethics committee may require direct access to parts of the medical records relevant to the study, including participants’ medical history.

2.9 Early Termination of the Study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of harm of the experimental intervention

2.10 Protocol Amendments

Substantial amendments are only implemented after approval of the CEC respectively.
Under emergency circumstances, deviations from the investigation plan to protect the rights, safety and well-being of human participants may proceed without prior approval of the CEC. Such deviations shall be documented and reported to the CEC as soon as possible.

All Non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3 INTRODUCTION

3.1 Background and Rationale

Anterior cruciate ligament (ACL) rupture is one of the most common and severe ligament injury [1], with around 250,000 to 400,000 patients per year diagnosed with ACL disruption in the United States [2-4]. Reconstruction of the ACL is currently recommended as the standard of care following an ACL tear or rupture [5]. There are a number of currently available graft choices for ACL reconstruction, including autografts, allografts, xenografts, and a variety of synthetic grafts [6-8]. Hamstring tendon autografts have emerged as the most widespread clinical choice, normally employed using either the semitendinosus tendon and/or gracilis tendon [9-11]. Despite the excellent mechanical characteristics of these ligament grafts, hamstring graft to bone healing is often poor, with tendon graft elongation or even pullout as common failure modes for hamstring graft reconstructions [12]. Additionally, hamstring tendon autografts have been associated with bone tunnel widening (BTW) [13-17]. Hamstring tendon autografts take a long time to be incorporated into the bone tunnel in order to provide sufficient mechanical strength [18]. To mitigate this poor graft-bone integration, many surgeons favor a bone patellar tendon bone (BPTB) autograft extracted from the middle third of the patellar tendon along with bone blocks in continuity at each end of the graft (blocks from tibial tubercle and the outer surface of the patella, respectively). Because the native bone-tendon interface in these grafts is quite strong, and bone-bone healing is rapid, clinical outcomes using these grafts are widely viewed as superior [19, 20]. The BPTB graft has for decades thus been regarded as a 'Gold Standard' graft choice for ACL reconstruction, among some controversy [21-25]. Still the BPTB autograft is severely limited by graft source site morbidity, with occasionally severe pain lasting up to 12 months after surgery – a fact that has drastically limited the use of BPTB autograft in the clinic [19, 26]. From a tissue engineering perspective, the largest challenge in reducing failure rates of hamstring tendon autografts is the integration of the graft with the host bone [27] with the long-term performance of the ACL graft believed to mainly depend on successful regeneration of the tendon-bone interface [28]. Many approaches have been tried to enhance the integration of the tendon-graft to bone in order to achieve improved biological attachment. The major concern is to provide appropriate molecular and cellular cues that result in effective healing between graft and bone. To this end, tissue engineering approaches have employed bone marrow derived mesenchymal stem cells (BMSCs) as potential agents to enhance graft to bone healing [29, 30]. Similarly, osteoinductive bioceramics such as Hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), brushite calcium phosphate cement (CPC) have also been adopted to augment graft to bone attachment [31-36]. In most approaches, classical fixation methods such as interference screws have been employed, despite their inherent limitations to providing osteogenic contact surfaces [35]. In the current approach, an osteoconductive scaffold (OCS) is enlaced into the quadrupled tendon graft and is intended to provide optimal contact between the hamstring tendon and osteoconductive surfaces (OCS or bone tunnel). The device under study is a composite material obtained using bovine bone-derived matrix reinforced with poly(L-lactide-co-ε-caprolactone) (PLCL) and polysaccharides [37]. It has been successfully used as a bone substitute for oral and maxillofacial reconstructive surgery. Its macro- and micro-porous structure similar to the structure of human bone promotes the formation and growth of new bone in the implant site. The combination of biopolymers and collagen derivatives facilitates blood retention and activates the cascade of regenerative signals in the defect site. Biopolymers and collagen derivatives are reabsorbed slowly over the course of several weeks while the substitute integrates with the receiving tissue

[IFU SmartBone]. The resorption and substitution of the OSC by bone close to the articular end of the bone tunnel should provide long-term fixation at a biomimetic attachment site of the ACL graft.

3.1.1 Bone Tunnel Widening following ACL-Reconstruction

BTW is a well-documented phenomenon following ACL-reconstruction [16, 38-40]. In studies using hamstring grafts, it has occurred in 25-100% in the femoral tunnel and in 29-100% in the tibial tunnel [41-45]. Although it may not affect the clinical outcome in terms of an increase in laxity or failure rates [46], it severely complicates revision surgery [40]. Etiological factors for tunnel widening probably are of mechanical, as well as of biological nature. Mechanical factors include motion of the graft within the bone tunnel, stress shielding and improper graft placement. Synovial fluid propagation into the bone tunnel and increased cytokine levels inducing osteolysis are believed to be biological factors leading to this phenomenon [40]. Bone tunnel widening can be assessed on plain radiograph [47], MRI [48] and CT with CT being the most accurate [49, 50]. In an attempt to reduce tunnel widening following ACL-reconstruction, osteoconductive materials have been used with promising results. The use of a poly-L-lactic acid (PLLA)-HA blended interference screw reduced tunnel widening compared to plain PLLA interference screws at an average follow-up of 30.9 months and 26.5 months, respectively (29.9 vs. 46% BTW) [46]. Similarly, Barth et al. [51] showed a statistically significant reduction of BTW using a poly (l-lactide-co-D,l-lactide) (PLDLLA)-HA/β-TCP composite screw compared to the polymer-only screw in the tibia, but not in the femur. PLLA/HA composite screws also outperformed metal interference screws for graft fixation in ACL-reconstruction in terms of BTW in a study conducted by Lind et al. [52]. Resorption of polymer-bioceramic interference screws however, is generally slow [53]. High mechanical loads during insertion do not allow the use of highly porous materials for interference screws. In the current application, the osteoconductive scaffold does not take primary fixation function. This allows the use of highly porous material.

3.2 Investigational Medical Device and Indication

The device under study is a bone substitute intended and specifically developed for bone regeneration applications [TechInfos SmartBone]. It is composed of a natural mineral matrix of bovine origin, reinforced with biodegradable synthetic polymers and natural collagen derivatives of bovine origin. It has a macro- and micro-porous structure similar to the structure of the human bone [IFU SmartBone].

Clinical studies were performed to assess osteointegration on a 4 months observation timeframe. Histological analysis confirmed osseous integration, with natural bone formation and cells and vessels colonizing pores within it during time. Summarizing, the main biological features are:

- high cell viability and proliferation support,
- high osteoinduction, conduction and integration.

Its mechanical properties can be summarized as follows:

- composite mechanical behavior: both rigid and elastic
- adequately high elastic modulus
- extreme load bearing resistance
- dust and debris free shaping
- capability to withstand precise shaping
- tenacity to fixation screws
- hammering and heavy surgical maneuvering resistance

3.3 Clinical Evidence to Date

3.3.1 SmartBone

Pre- and post-market clinical investigations to date using SmartBone were performed only in the field of oral, maxillofacial and cranial surgery. The rationale behind this focus was that findings regarding performance and safety of a bone graft in said fields can be transferred to the use of the device in all orthopedic applications, but that vice-versa conclusions are not possible.
In the following, clinical study data regarding SmartBone are summarized.

Study design	**No. of pat.**	**Aim**	**Setup**	**Results**
Single-centre, non-randomized, comparative clinical trial [37].	5	Assessment of complete *in vivo* biocompatibility and efficacy.	Comparison of the non-CE marked device with its CE marked raw material component Tutobone (Tutogen, Germany).	Histological analyses confirmed osteointegration and remodeling capabilities.
Post-market clinical follow-up. Randomized, non-blinded, multi-centric clinical trial (not published yet).	44	Confirm clinical performance and safety throughout a meaningful observation period.	17 investigators performed surgeries in oral, maxillofacial and cranial districts. Quantitative assessment of bone regeneration based on evaluation of grafted volume evident on radiographs.	27 patients monitored over the entire time frame (1 year). Out of the total of 44 patients:12 cases showed optimal regeneration.29 showed good regeneration. 3 showed medium regeneration. No failures, no accidents, nor adverse events nor poor results were recorded.
Monocentric cohort study [54].	62	Confirm safety, performance and acceptability of identified residual risks	Monitoring safety and performance outcome using quantitative assessment of bone regeneration based on evaluation of grafted volume evident on radiographs.	60 patients monitored over the entire time frame (>1.5 years). 55 cases showed optimal regeneration. 1 case with good regeneration. 3 cases with poor regeneration. 1 case with a reported failure for dehiscence. No further failures, no accidents, nor adverse events nor poor results were recorded. The clinical data confirmed safety and performance of the device and showed acceptability of residual risk.

Histological investigation [55].	10	Assess the mechanism of action of the device histologically.	Collection of tissue biopsies from clinical cases allowing easy and precise sample collection. Histomorphometric analysis and bone-particle conductivity index calculation.	Based on the analysis of 6 histological images it was concluded that the bone graft shows about 35 – 40% substitution at about 4 – 8 months and complete substitution after about 2 years. No inflammatory cells were detected, confirming full biocompatibility of the medical device.
Multicenter prospective clinical trial (not published yet)	58	Evaluation of the newly-formed tissue, correlating clinical and histological results to the sinus cavity size and conformation.	Transcrestal sinus floor elevation performed in atrophic ridges. Cone beam computed tomography 10 days and 6 months after surgery. After 6 months a bone-core biopsy was harvested. Histomorphometric analysis was conducted.	56 cases showed good or optimal regeneration. 2 cases with failure for dehiscence. No further failures, no accidents, nor adverse events nor poor results were recorded.
Monocentric cohort study (not published yet)	10	Histomorphometric evaluation.	Alveolar preservation after tooth-extraction. Collection of biopsies 4 months after implantation. Comparison of histological images with known cases treated with with other commercially available bone substitutes.	Biopsies collected at 4 months post-implantation showed the contemporaneous presence of SmartBone, new bone and fibrous tissue wirh formation of new vessels. Bone ECM molecules were highly expressed in the newly formed bone and osteoblasts were visible on the device's surfaces. No failures, no accidents, nor adverse events nor poor results were recorded.

3.3.2 Autograft Scaffolds for ACL-Graft Fixation

Kim et al. [56] prospectively reviewed 81 patients who had undergone ACL-reconstruction with an Achilles tendon allograft using a bioabsorbable interference screw (group I) or an autogenous bone plug harvested from the tibial bone tunnel (group P) for tibial graft fixation. Patients and outcome-assessors were blinded to group assignment. After an average follow-up of 7.5 years, complication rate in group P was significantly less frequent than in group I (6 vs. 14) and tunnel widening, assessed as cross-sectional area on MRI, averaged 15% in group P and 38% in group I ($p = 0.017$). No significant changes for patient subjective outcome scores

and stability were detected. The authors deemed the use of autograft bone plugs for graft-fixation a reasonable option for ACL-reconstruction with Achilles tendon allograft.

3.3.3 Xenograft Scaffolds for ACL-Graft Fixation

The bovine bone matrix SmartBone consists of is a CE-marked product (Tutobone) by Tutogen, Germany. In a randomized controlled trial, Jagodzinski et al. [57] used Tutobone, shaped into a conical block, for tibial press-fit fixation of the hamstring autograft in ACL-reconstruction. This approach was compared to the traditional technique using bioresorbable interference screw fixation, in terms of clinical outcome and BTW. At the proximal section of the tibial bone tunnel, the tunnel diameter was significantly smaller for the press-fit group at 3, 6, 12 and 24 months follow-up. No significant differences were detected for IKDC-, Tegner-, Lysholm score and knee stability between the two groups. No intra- or postoperative complications were reported.

3.3.4 Adverse Device Effects

In 2008, Konan et al. [58] summarized the literature concerning adverse device effects associated with the use of bioabsorbable interference screws in ACL-reconstruction. Adverse device effects identified, related to composite screws containing a part bioceramic (β-TCP/HA), were:

- Screw breakage during insertion
- Subcutaneous cyst formation (cured within the following 3 months)

Tecklenburg et al. [59] evaluated the clinical outcome of ACL-reconstruction using hydroxyapatite composite screws, β-TCP composite screws and allograft interference screws in a total of 60 patients. There was no inflammatory response noted in any patients.

3.4 Rationale for the Intended Purpose in Study

The clinical outcome of ACL-reconstruction depends on the successful integration of the tendon-graft into the host bone close to the attachment site of the native ACL [60-62]. The OCS is enlaced into the tendon-suture construct and provides an osteoconductive / osteoinductive environment at the articular aperture of the bone tunnel. The design maximizes the contact area between tendon and osteoconductive surface (Bone/HA). Different to the application of interference screws, graft insertion exerts minimal stress on the insert and allows the use of highly porous material. Enhanced bone-tendon integration should reduce graft micromotion and increase the repair strength of the reconstructed ACL. This in turn should reduce the rate of graft failure and the incidence of tunnel widening.

3.5 Explanation for Choice of Comparator

The active comparator in the current study will be the standard ACL-reconstruction technique used at Balgrist University Hospital.

3.6 Risk / Benefits

Since the OCS is an approved, CE-marked device, product related risks like biocompatibility, shelf-live et cetera were excluded from the internally conducted risk assessment and possible adverse effects of the product can be seen in the instruction for use.
However a careful and detailed risk assessment was performed according to EN ISO 14971:2013-04 to also take overall - not only product related risks into account.

To identify and evaluate the risks a Failure Mode and Effects Analysis (FMEA) was performed, based on EN ISO 14971:2013-04 Annex C informative guideline.
The full FMEA can be delivered upon request. In the following the results of the investigation are summarized. Identified risks in *italic.*

Clinical study related risks

- *Surgical team (surgeons, staff) is not introduced to clinical study procedure (device is not used according to study protocol).* This risk has been minimized by several pre-clinical cadaver tests, where the full intervention was carried out, documented and analyzed with the involved team. (KEK-ZH-Nr. 2015-0372, Developing a novel surgical procedure for improved ACL reconstruction).
- *Logistical flow from producer to patient does not work*. Involved staff is informed and used to handling and storage conditions of the different medical products used for this study (OCS, sutures).
- *Soft tissue bridging during graft insertion*. In performed cadaver tests a possible soft tissue bridging which can occur during graft insertion through the medial portal did not occur. Since the graft insertion is reversible until knots are fastened this issue can be solved intraoperatively.
- *OCS breaks during graft insertion. In-vitro* experiments were performed in order to assess device strength during surgical insertion. For femoral pull-in of the construct, a force of 250N was applied resembling maximal achievable voluntary one-handed force. Subsequently, the construct was extracted and inspected for damage. None of the samples showed damage to the OCS.
- *ACL loads during rehabilitation lead to damage to OCS and to subsequent release of particles into the joint capsule*. The laboratory of Orthopedic Biomechanics at ETH Zurich performed mechanical *in-vitro* testing on the construct under study in porcine knees. The experiment included high load – low cycle testing, simulating out of the ordinary situations such as stumbling or jumping, as well as low load – high cycle testing, simulating the long term mechanical environment during rehabilitation. The OCS performed well in all tests with no signs of abrasion particles being released from the construct.
- *OCS inserted into the tendon-graft reduces the fatigue life of the graft-construct.* The material properties of the OCS highly differ from the material properties of the surrounding tendon. The OCS might damage the tendon or the suspension suture and accelerate fatigue failure of the construct. Comparing the fatigue life of the construct with OCS and without OCS revealed no such effect.

The overall risk of this study is therefore stated as very low and has been evaluated acceptable, the expected benefits overweigh the minimized residual risk.

Expected Benefits:

- Faster healing of soft-tissue to bone (up to 3-times more tendon to bone surface area)
- Stronger secondary fixation by having a „bony bridge“
- Reduced tunnel widening due to faster secondary fixation (bone to bone) and windshield wiper effect.
- A successful outcome of this study would have a big impact in an improved ACL reconstruction. Further studies for a tibial (femoral & tibial) solution could be carried out on the basis of this study.

3.6.1 Radiological Assessment Related Risks

The mean volume CT dose index and the dose-length product of one CT-scan of the knee are approximately 9.8 mGy and 189 mGy*cm respectively. Using an effective dose conversion

coefficient of 0.0004 mSv/(mGy*cm) for the knee of an adult subject [63] yields an effective radiation dose of 0.0756 mSv per examination.
According to the reference table provided by Swissethics, one plain radiography examination of the knee in anterior-posterior direction yields an effective radiation dose of 0.015 mSv [64].

The table below shows the calculation of the total effective radiation dose each participant is exposed to by the two measurement modalities used in the current study [65].

Measurement modality	Effective dose per examination [Millisievert]	Number of examinations per subject	Total effective radiation dose per subject [Millisievert]
Computed Tomography	0.0756	3	0.2268
Plain Radiology	0.015	5	0.075
Total exposure			**0.3018**

3.6.2 Anticipated Adverse Device Effects

Anticipated adverse device effects based in part on the literature search described above are the following.

- Subcutaneous cyst formation
- Intratunnel cyst formation [66]

Subcutaneous cysts usually reside over time and are easily manageable surgically [66, 67]. Intratunnel cysts are related to the effect of BTW and are therefore subject of the current investigation.

4 STUDY OBJECTIVES

4.1 Overall Objective

The overall objective of this study is to evaluate the efficacy of the use of the OCS in ACL reconstruction.

4.2 Primary Objective

The study seeks primarily to determine the effect of the use of the OCS-autograft fixation construct on femoral bone tunnel widening compared to the traditional ACL-reconstruction technique using a hamstring autograft.

4.3 Secondary Objectives

Secondary objectives are to assess patient subjective measures of knee function and objective measures of knee stability of the interventional treatment compared to the control treatment. Also the success of return to pre-injury activity level will be assessed. Additionally OCS-bone integration will be investigated.

4.4 Safety Objectives

Safety will be evaluated by the occurrence, frequency and severity of intra- and postoperative complications.

5 STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome variable of this study is the relative change of the CT evaluated femoral bone tunnel volume from baseline to follow-up at 12 months.
As the primary objective of the use of the OCS is to reduce tunnel widening by promoting bony ingrowth into the bone tunnel, the relative change of bone tunnel volume over time is an appropriate measure to quantitatively assess this effect. Assessing relative changes as opposed to absolute values negates the potential for bias by different tunnel drill sizes used in the two treatment arms potentially influencing the absolute ossification/de-ossification. In quantifying bone tunnel size, CT measurements provide substantially more reliable means than plain radiography or magnetic resonance imaging [50, 68].

5.2 Secondary Outcomes

The secondary endpoints aim to assess the clinical outcome of the two treatment groups. These clinical outcome measures can be divided into two domains: Patient subjective knee function and objective measures of knee stability.

5.2.1 Patient Subjective Knee Function

Patient subjective knee function is assessed using the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form (SKEF) and the Lysholm Knee Scoring Scale (LKSS) measured at baseline visit (surgery) and at each follow-up visit.

5.2.1.1 IKDC Subjective Knee Evaluation Form

IKDC SKEF is designed to detect improvement or deterioration in symptoms, function and sports activities due to knee impairment for patients with a variety of knee conditions including ligament injuries. It is a patient-completed questionnaire available in multiple languages including German with an ordinal scoring system ranging from 0 (highest level of symptoms or lowest level of function) to 100 (no limitation with daily or sporting activities and the absence of symptoms) [69].

5.2.1.2 Lysholm Knee Scoring Scale

LKSS is designed to evaluate outcomes of knee ligament surgery, particularly symptoms of instability [70]. It has an ordinal scoring system ranging from 0 to 100 (No symptoms or disability) [71]. A validated German version will be used [72].

5.2.2 Objective Measures of Knee Stability

Anterior laxity is evaluated using the KT-1000 Arthrometer Test and the Lachman Test. Rotational stability is assessed using the Pivot Shift Test.

5.2.2.1 KT-1000 Arthrometer Test

The KT-1000 Arthrometer Test measures anterior displacement of the tibial plateau on the femur at a specific force. Its output variable is defined as the difference in full millimeters between the tibial displacement of the ACL reconstructed knee and the normal contralateral side [73].

5.2.2.2 Lachman Test

The Lachman test measures anterior displacement conducted manually by the clinician. It is graded as the difference from the normal contralateral side as 0 (<3 mm), 1 (3 to 5 mm), or 2 (>5 mm) [74].

5.2.2.3 Pivot Shift Test

The pivot shift test assesses the combined tibio-femoral rotation and anterior tibial translation. The pathologic motion elicited is graded as a glide (grade 1), clunk (grade 2), or gross clunk with locking (grade 3). A normal finding is graded as zero. The grade of the pivot shift has been shown to correlate with patient-reported functional instability and clinical outcomes [75]. The outcome measure is calculated from the difference between affected (repaired) and intact knee.

5.2.2.4 Tegner activity scale

The Tegner activity scale (TAS) is used to measure the change in physical activity from pre-injury to follow-up. It was designed to complement the functional outcome of the LKSS. Patient's activity is scored on a scale with 11 levels from level 0 (on sick leave/disability) to level 10 (participation in competitive sports such as soccer at a national or international elite level) [71]. Evaluated will be the difference in score from pre-injury (assessed at baseline visit) to follow-up.

5.3 Other Outcomes of Interest

5.3.1 Patient History

Patient history will be assessed using an adapted version of the IKDC SKEF (German version). Assessed will be:

- Date of injury
- Affected knee
- Activity of injury
- Mechanism of injury

5.3.2 OCS-Bone Integration

For a quantitative analysis of OCS-bone integration, the mineral density profile along a predefined line will be examined. A slice showing the central portion of the OCS in the axial plane will be selected. A straight line of 2 cm length will be drawn perpendicular to the long axis of the OCS using image analysis software (Mimics). The CT-values along this line will be recorded and evaluated in the following way. Since the CT-values change according to the bone mineral density, the profile along the line will have a minimum at the interface of the tunnel wall and the OCS and a maximum on the OCS. The difference in Hounsfield units from the cancellous bone in the tunnel wall and the OCS-bone interface will be used as a measure for the degree of osseous integration of the implant [24].

5.3.3 Intra-Patient Comparison of Ossification

The intervention group will be additionally assessed in an intra-patient comparison model [51]. Using the available CT data, the tibial bone tunnel volume will be calculated using the same method as for the femoral bone tunnel volume described below. The relative change of the two parameters will be compared.

5.3.4 Plain Radiography assessed Bone Tunnel Widening

BTW will additionally be assessed on plain radiograph. Standard posteroanterior radiographs of the knee in full extension will be used [76]. Bone tunnel width will be assessed at the widest part of the femoral bone tunnel. Assessed will be the relative change in femoral bone tunnel width.

5.4 Safety Outcomes

Any occurrence of intra-operative complications will be recorded on the eCRF. Post-operative (serious) adverse events will be recorded at each follow-up visit.

6 STUDY DESIGN AND COURSE OF STUDY

6.1 General study design and justification of design

The present study is designed as a randomized patient-blinded equally sized two-group parallel design superiority trial using an active comparator. ACL-reconstruction using the in-house standard of care will be compared to the method under investigation. In a two staged randomization, a total of 56 patients are assigned to either of the two treatment groups.

6.1.1 Time Frame of the Study

Currently, no precise time frame for the occurrence of BTW has been defined [41]. Chen et al. [77] investigated the incidence of BTW following ACL-reconstruction using hamstring tendon in 58 patients at 1, 2, 3, 6, 12 and 24 months postoperatively. BTW was found to mainly occur during 3 to 6 months after surgery with no change in bone tunnel volume between 12 and 24 months postoperatively. Similarly, Jo et al. [78] concluded, BTW to be maximal within the first 9 months following surgery using patellar tendon grafts. For the current trial, BTW-assessment using CT-scanning 4.5 and 12 months after surgery seems therefore reasonable. The need of correlating BTW with long-term clinical results has also been pointed out [79].

6.2 Study Duration and Study Schedule

Total duration of subject participation will be 5 years. Total duration of the study is expected to be 82 months. Duration of patient acquisition is hereby estimated to be 22 months. This estimate is based on the following assumptions:

- ACL-reconstruction surgeries performed monthly at the investigation site: 12
- Ratio of patients agreeing to participate: 60% (estimate based on internal data)
- Ratio of patients eligible for the study: 35% (estimate based on internal data)

The estimated patient allocation rate is therefore:
12/month * 0.6 * 0.35 = 2.52/month
Estimated duration for the acquisition of 56 patients is 22.2 months.

First-Patient-In: 07/2017
Last-Patient-Out: 04/2024
Statistics/Abstract: 12/2024

6.3 Methods of Minimizing Bias

6.3.1 Randomization

A two-staged randomization method will be used. To ensure adequate treatment distribution for interim analysis, the first block will contain 10 interventional and 10 control treatments. In the following, a block for the remaining treatment allocations will be used.

6.3.2 Blinding Procedures

The current clinical trial is designed as a patient-blinded study.
Group allocation cannot be blinded to the operateur nor can the group allocation be blinded to the practitioner evaluating the radiological images at regular postsurgical follow-up visit and for safety assessment.
Concealment of group allocation to the patient is ensured. During surgery, graft preparation and graft insertion is outside the patient's field of view.
No radiological images will be shown to the patient as to not reveal group allocation.

6.3.3 Other Methods of Minimizing Bias

Patient subjective knee function will be assessed using German versions of validated questionnaires [69, 72]. KT-1000 arthrometer testing provides the means to objectively measure anterior knee stability [80].

6.4 Unblinding Procedures

At patient study end - planned or unplanned - the patient will be informed about his/her group allocation in the trial.

7 STUDY POPULATION

7.1 Eligibility criteria

7.1.1 General Criteria for Eligibility

Participants fulfilling all of the following criteria are eligible for the study:

- 18 to 60 years of age at entry.
- Males and females.
- An ACL insufficiency as determined by clinical examination (positive pivot shift and/or positive Lachman test).

The presence of any of the following criteria will render the patient not eligible for the study:

- Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to the investigational product,
- Women who are pregnant or breast feeding,
- Medical condition or comorbidity that would interfere with study participation.
- Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.),
- Acute or chronic infections (i.e. osteomyelitis) in the surgical site,
- Uncontrolled metabolic diseases, such as diabetes, osteomalacia, thyroid dysfunctions,
- Long-term cortisone therapy,
- Autoimmune diseases,
- Radiotherapy,
- Heavy smokers,
- Motion disorder,
- Known or suspected non-compliance, drug or alcohol abuse,
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
- Participation in another study with investigational drug within the 30 days preceding and during the present study,
- Previous enrolment into the current study,
- Enrolment of the investigator, his/her family members, employees and other dependent persons.

7.1.2 Inclusion / Exclusion for Eligible Subjects

Eligible patients fulfilling all of the following inclusion criteria will be included into the study:

- Patient has reached skeletal maturity

- A complete ACL tear to be reconstructed using hamstring tendon autograft. The ACL injury can either be isolated or combined with one or several of the following injuries:
    - A meniscus tear that is either left untreated or treated with partial resection,
    - A small, stable meniscus tear treated with fixation, but fixation not interfering with the rehabilitation protocol,
    - Cartilage changes verified on MRI with arthroscopically determined intact surface or fissuring on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter (Outerbridge grade I-III [81]).
- Harvested folded tendon (unsutured) has a diameter between 8 and 8.5mm at the end to be inserted into the femoral bone tunnel determined using a tendon thickness tester (Karl Storz).
- Tendon graft construct consists of one of the following:
    - Semitendinosus tendon quadrupled
    - Semitendinosus tendon quadrupled plus gracilis tendon doubled
    - Semitendinosus tendon doubled plus gracilis tendon doubled
- A normal joint status possibly combined with either one of the following findings:
    - A small-avulsed fragment located laterally, usually described as a Segond fracture,
    - Joint space narrowing grade 1 or osteophytes grade 1 as determined by the OARSI atlas [82].
- Informed Consent as documented by signature

Eligible patients fulfilling any of the following criteria will be excluded from the study:

- Prior fracture of the affected leg,
- Earlier major knee injury to the index knee,
- Associated posterior cruciate ligament injury or medial collateral ligament injury grade III in index knee,
- Previous or current ACL injury on contra-lateral leg,
- One of the following injuries to the index knee as visualized on MRI and/or arthroscopy:
    - An unstable longitudinal meniscus tear that requires repair and where the following treatment interferes with the standard rehabilitation protocol,
    - Bi-compartmental extensive meniscus resections,
    - A cartilage injury representing a full thickness loss with exposed subchondral bone (Outerbridge classification grade IV),
    - A total rupture of the lateral collateral ligament.
- Diameter of the tendon graft does not allow the use of the OCS (Irrespective of group allocation).
- Poor bone quality / missing bone material requiring alternative / additional graft-fixation.

7.2 Recruitment and Screening

Patients who will undergo ACL-reconstruction at Balgrist University Hospital will be recruited for this trial. All patients will be informed about the purpose of the trial, the operation modalities, and their benefits as well as risks. Patients will be asked whether they are prepared to participate in the trial prior to their inclusion. The patients will be handed out the written patient information brochure and will be given a minimum of 7 days for consideration. Patients that gave written informed consent will be screened for the inclusion and exclusion criteria of the current trial. Patients who were screened but not enrolled in the trial (including patients unable to give informed consent due to any reason) will be documented in the screening log, recording the reason for exclusion.
All travel expenses for study-visits outside of standard of care will be reimbursed in the following way:

- Public transportation ticket from domicile to study site and back (2. Class, no Halbtax), or

- In case of travel by car: 0.50 CHF per kilometer from domicile to study site and back.

Study-visits outside of standard of care and therefore object of reimbursement are: Visit 6 and 7.

7.3 Assignment to Study Groups

A two-staged randomization scheme will be used. The first block will contain a total of 20 patients. The second block will contain a total of 36 patients. For each block, a container with sealed envelopes with paper cards for the group assignment (equally sized groups) will be prepared. At final inclusion of a patient, one sealed envelope will be drawn from the container and the patient will be assigned accordingly. After assignment, the paper cards are sealed again and stored in the patients case report file.

7.4 Criteria for Withdrawal/ Discontinuation of Participants

If during the course of the study, a participant meets an exclusion criterion, he will be withdrawn from the study. Specifically, a potential rerupture of the graft will lead to exclusion of the patient. In any case of premature discontinuation of a participant, the reason will be documented in the respective eCRF.

8 STUDY INTERVENTION

The surgical intervention under study is described in detail in ACLROCS_ WI_InterventionalSurgicalTechniqueGuide.

8.1 Femoral Fixation Construct

Control Group: Doubled suture loop (Ethibond 6) at appropriate length determined intra-operatively connected to the femoral cortical fixation button (Flipptack, Karl Storz).
Intervention Group: Doubled suture loop (Ethibond 6) at appropriate length determined intra-operatively connected to the femoral cortical fixation button (Flipptack, Karl Storz). This construct is additionally connected to the device under study according to the interventional surgical technique guide.

8.2 Graft Preparation

Tendon preparation is done according to the in-house standard technique [Zeichnung SemiT-G-Transplantatvorbereitung Flipp-Endotack_Balgrist]. The following procedures apply for both groups under study. Three graft configurations are permitted for study inclusion. In the following, the specifics in graft preparation related to tendon configuration are outlined.

8.2.1 Semitendinosus Tendon-only Graft

The semitendinosus tendon is harvested intra-operatively as described in the following chapter. The harvested tendon is mounted on the tendon board (Karl Storz) and both tendon ends are sutured using baseball stitches (Fibre Wire 2). The tendon is folded around a doubled suture (Ethibond 6). The tendon is folded a second time and enlaced with the femoral fixation construct. The tibial fixation button (ENDOTACK®, Karl Storz) is inserted and the construct is mounted on the tendon board (Karl Storz). Three sutures are placed on the tibial side of the graft and three on the femoral side in order to create a self-reinforcing suture noose (Vicryl 2-0).

8.2.2 Doubled Semitendinosus – Doubled Gracilis Tendon Graft

The harvested semitendinosus tendon is combined with a doubled gracilis tendon due to insufficient tendon length. The tendon ends are sutured using baseball stitches and the tendons are enlaced with the femoral fixation construct. Final graft preparation is then performed equivalently to the technique using semitendinosus tendon only.

8.2.3 Quadrupled Semitendinosus – Doubled Gracilis Tendon Graft

The harvested semitendinosus tendon is combined with a doubled gracilis tendon due to insufficient tendon diameter. The tendon ends are sutured using baseball stitches and the semitendinosus tendon is folded once. The two tendons are then enlaced with the femoral fixation construct. Final graft preparation is then performed equivalently to the technique using semitendinosus tendon only.

8.3 Bone Tunnels

The harvested unsutured tendon-graft must measure between 8 and 8.5 mm in diameter at the end to be inserted into the femoral bone tunnel for subject inclusion (see chapter 7.1.2). Enlacing the OCS increases the graft diameter by 1 mm (Determined experimentally).

Accordingly, the overdrilled socket of the femoral bone tunnel has the following diameter depending on the subject's group assignment:

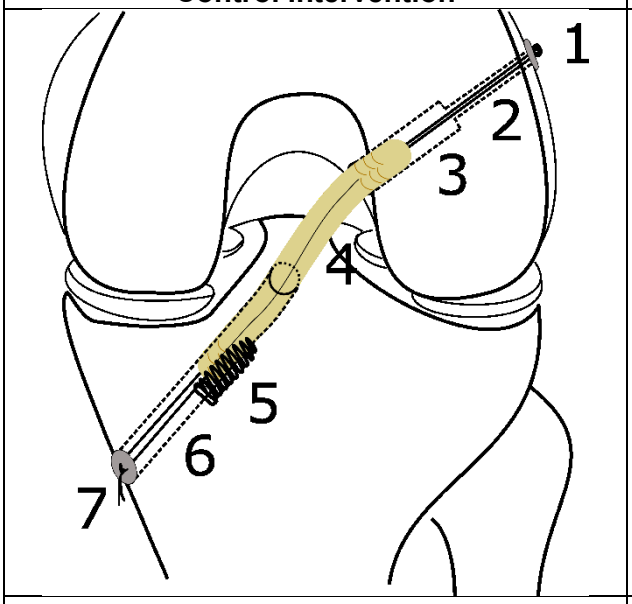
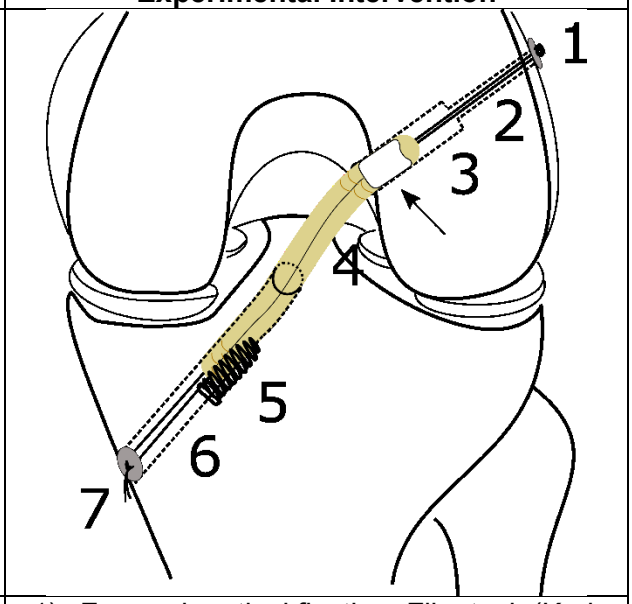
- Intervention group: 9 - 9.5 mm
- Control group: 8 – 8.5 mm

The tibial bone tunnel is drilled at a diameter of 8 ± 1 mm as applicable.

8.4 Surgical Technique

The surgical technique under study uses a semitendinosus tendon autograft (combined with gracilis tendon if applicable) harvested from the index knee or the contralateral knee according to the standard in-house technique. The pes anserinus is visualized through a three centimeter incision anteromedially at the proximal tibia. The semitendinosus tendon is harvested with a tendon stripper and length and thickness is measured. For the intraarticular procedure, standard medial and lateral parapatellar arthroscopy portals are used. After overdrilling with a 4.5 mm drill, the final femoral graft tunnel is created by a cannulated drill. Afterwards the tibial tunnel is prepared by using a drillguide (Karl Storz, Tuttlingen, Germany) targeted at the center of the tibial ACL footprint. The tendon graft is inserted first into the femoral bone tunnel through the medial portal. In the femoral tunnel the graft is secured using a flipping device on the cortical bone (Flipptack, KarlStorz, Tuttlingen, Germany). Tibial graft-fixation is achieved using an interference screw (Megafix, Karl Storz, Tuttlingen, Germany) proximally, and a small plate (Endotack, Karl Storz, Tuttlingen, Germany) covering the bone tunnel distally.

The table below shows a schematic of the surgical techniques for graft fixation under study and the material in use.

Control Intervention	Experimental Intervention
	
1) Femoral cortical fixation: Flipptack (Karl Storz) 2) Femoral Graft suspension: Ethibond 6 (Ethicon Inc.) Suture bone tunnel; diameter: 4.5 mm 3) Cannulated bone tunnel; diameter: 8 – 8.5 mm Length: 27 mm 4) Tendon graft 5) Resorbable interference screw fixation (Megafix, Karl Storz) 6) Tibial bone tunnel; Diameter: 8 – 8.5 mm Tibial Graft suspension: Fibre Wire 2 (Ethicon Inc.) and Ethibond 6 7) Tibial cortical fixation: Endotack (Karl Storz)	1) Femoral cortical fixation: Flipptack (Karl Storz) 2) Femoral Graft suspension: Ethibond 6 (Ethicon Inc.) Suture bone tunnel; diameter: 4.5 mm 3) Cannulated bone tunnel; diameter: 9 – 9.5 mm Length: 27 mm 4) Tendon graft 5) Resorbable interference screw fixation (Megafix, Karl Storz) 6) Tibial bone tunnel; Diameter: 8 – 8.5 mm Tibial Graft suspension: Fibre Wire 2 (Ethicon Inc.) and Ethibond 6 7) Tibial cortical fixation: Endotack (Karl Storz) Black Arrow: Medical device under study enlaced into tendon graft.

8.4.1 Interventional Product

Brand name	SmartBone®
Type	Block BTB-Converter
Dimensions	8x11 mm
Manufacturer	Industrie Biomediche Insubri
Description	SmartBone® is a composite xeno-hybrid Class III CE marked Medical Device, composed of bovine-bone derived porous mineral matrix, reinforced with a blend of collagen fragments (in the form of hydrolysed gelatine) and biopolymers (i.e. resorbable aliphatic block-co-polyesters), intended for use in bone regeneration applications in reconstructive surgeries. SmartBone® is a long-term implantable, resorbable, sterile medical device, which is supplied in different shapes and dimensions to best match surgical needs. From big (15 x 30 x 60 mm^3) solid blocks to granulates (1-2 mm and 2-4 mm) to fine microchips (0.25-1mm).
Intended use (according to IFU)	SmartBone® is recommended for reconstructing and filling bone defects and for bone augmentation. For example, SmartBone® is recommended for filling bone defects and for bone augmentation in the following cases: • Augmentation/reconstruction of the alveolar ridge; • Alveolar filling after extraction; • Implants: preparation of the implant bed, filling of the bone dehiscences, augmentation of the sinus floor; • Periodontology: filling of bone defects, providing support for the membrane in guided tissue regeneration (GTR).
Intended user and patient population	SmartBone is intended for professional use only. It should be used by trained surgeons, e.g. orthopedic surgeons, neurosurgeons, plastic surgeons, oral and maxillofacial surgeons and trained dentists. The patient population consist of adults (age 18+; skeletally mature subjects) with edentulous areas or bone defects.
CE Declaration of Conformity	Yes
Device Materials	Bovine derived matrix: • Calcium hydroxyapatite ($Ca_5(PO_4)_3(OH)$) • Minor collagen residuals Coating: • Poly(L-lactide-co-ε-caprolactone) • Polysaccharides

8.4.2 Packaging, Labelling and Supply (Re-Supply)

Upon receipt of the study device supplies, an inventory must be performed and a device receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files.

Regular study device reconciliation will be performed to document assigned and used devices. This reconciliation will be logged on the device accountability form, and signed and dated by the study team.

8.4.3 Storage Conditions

The device under study is stored in a secure, limited access area under the recommended storage conditions. It is to be stored in its original package in a dry place and away from direct sources of light or heat at temperatures between 2 and 25°C.

8.5 Modifications of Device Application

Modifications of the device under study or of its application are not planned.

8.6 Compliance with Study Intervention

No postsurgical exclusion criteria related to patient compliance are defined.

8.7 Data Collection and Follow-up for Withdrawn Participants

For subjects who withdraw from the study prior to completion, the site will attempt to contact the subject in order to obtain safety information.

8.8 Trial Specific Preventive Measures

In case of complications during ACL-reconstruction using the investigational product, the standard technique will be applied. The patient will be excluded from further analysis, the reason for exclusion will be recorded. Before every CT-scan, female patients will undergo pregnancy testing. Female patients of child bearing potential will have agreed in the informed consent form, to use contraception during the first 24 months of the study.

8.9 Concomitant Intervention(s)

Allowed concomitant surgical interventions are defined in the inclusion/exclusion criteria and will be recorded in the eCRF. No specific postsurgical concomitant rehabilitation therapies are prohibited. The patient will be advised to inform the treating physician about the participation in the clinical trial in the case he receives treatment - related or unrelated to the intervention under study – outside of the study protocol.

8.10 Medical Device Accountability

The investigator will maintain records including date of receival, lot number and quantities of the medical device under study.

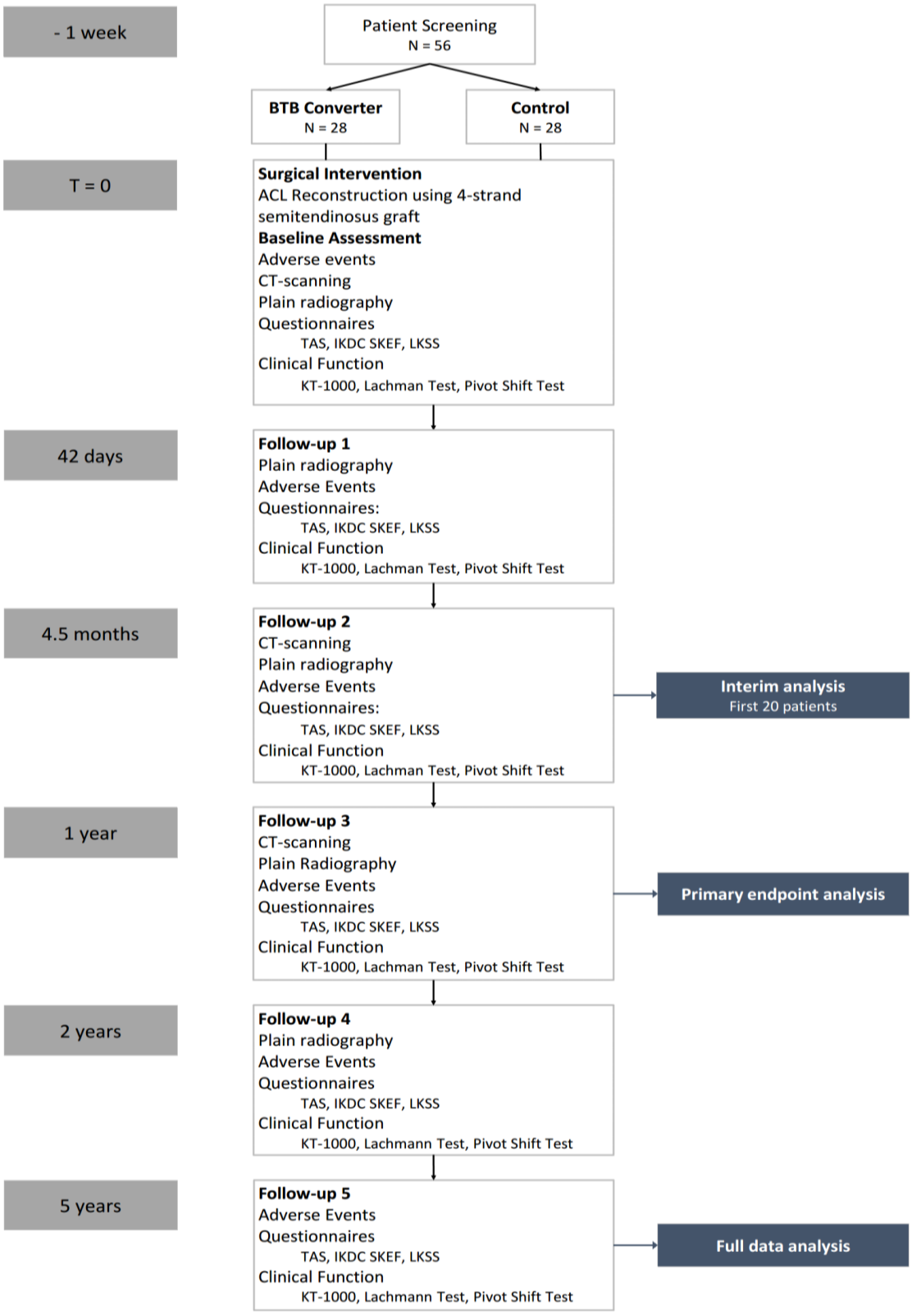
8.11 Return or Destruction of Medical Device

At completion of the study, there will be a final reconciliation of devices shipped and used. This reconciliation will be logged on the device accountability form, signed and dated. Any

discrepancies noted will be investigated, resolved, and documented prior to return or destruction of study devices. Devices destroyed on site will be documented in the study files.

9 STUDY ASSESSMENTS

9.1 Study Flow Chart



9.2 Assessments of Outcomes

9.2.1 Assessment of Primary Outcome

Bone tunnel volume will be assessed on CT. CT-scanning will be overseen by an experienced radiologist. The procedure (including pregnancy testing) is described in more detail in ACLROCS_WI_CTScan. The DICOM (Digital Imaging and Communications in Medicine) series are converted into a single volume and cropped to include the distal femur. Subsequently, the follow-up volumes of each patient are volumetrically registered to the baseline volume by using a rigid affine mutual information algorithm [83]. An intensity-based mask of each volume is created and cropped to contain only the femoral bone tunnel. The voxel-based volume of each follow-up mask is determined and compared to the baseline volume. The procedure is described in detail in ACLROCS_WI_FemBoneTunVolCalc.

9.2.2 Assessment of Secondary Outcomes

9.2.2.1 Assessment of Patient Subjective Knee Function

IKDC SKEF, LKSS and TAS are assessed with patient filled eCRFs using online surveys on a tablet computer. The procedure is conducted by the SN.

9.2.2.1.1 IKDC Subjective Knee Evaluation Form

IKDC SKEF contains a total of 16 items. The responses to each item are scored using an ordinal method such that a score of 0 is given to responses that represent the lowest level of function or highest level of symptoms. The IKDC SKEF score is calculated by summing the scores for the individual items and then transforming the score to a scale that ranges from 0 to 100. The maximum possible item score is 87. IKDC SKEF score therefore is calculated as follows:

$$\text{IKDC SKEF Score} = \frac{\text{Sum of item scores}}{87} \times 100$$

9.2.2.1.2 Lysholm Knee Scoring Scale

LKSS contains a total of 8 items. Each item response is scored based on the table shown below. LKSS score is calculated by summing up all item scores. The range of possible total score is [0,100].

Symptoms	Options	Points
Hinken	kein	5
	leicht oder gelegentlich	3
	stark oder konstant	0
Hilfsmittel	keine	5
	Stock oder Unterarmgehstütze	2
	Belastung unmöglich	0
Blockieren	kein Blockieren und kein Gefühl des Einklemmens	15
	Gefühl des Einklemmens aber kein Blockieren	10
	gelegentilches Blockieren	6
	regelmässiges Blockieren	2
	blockiertes Gelenk bei der Untersuchung	0
Instabilität	niemals "giving way" (=einknicken)	25
	selten während des Sports oder anderer starker Anstrengung	20
	regelmässig während des Sports oder anderer starker Anstrengung (oder Teilnahme unmöglich)	15
	gelegentlich bei Alltagsaktivitäten	10
	oft bei Alltagsaktivitäten	5
	bei jedem Schritt	0
Schmerzen	keine	25
	nicht immer und leicht während starker Anstrengung	20
	deutlich während starker Anstrengung	15
	deutlich während oder nach mehr als 2 km gehen	10
	deutlich während oder nach weniger als 2 km gehen	5
	konstant	0
Schwellung	keine	10
	bei starker Anstrengung	6
	bei gewöhnlicher Anstrengung	2
	konstant	0
Treppensteigen	keine Probleme	10
	leicht eingeschränkt	6
	Stufe für Stufe	2
	unmöglich	0
Kniebeugen (in die Hocke gehen)	kein Problem	5
	leicht eingeschränkt	4
	nicht mehr als 90°	2
	unmöglich	0

9.2.2.1.3 Tegner Activity Scale

TAS contains one item. It is scored based on the following table. At surgery visit (Visit 2), preinjury activity score will be assessed.

Instructions	Choice	Score
Die folgende Frage bezieht sich auf Ihr Aktivitätsniveau. Bitte lesen sie die nachfolgende Aufstellung durch und kreuzen das HÖCHSTE Level an, das auf Sie zutrifft.	Fussball	10
	Eishockey, Ringen, Turnen, Fussball (untere Ligen)	9
	Skifahren, Badminton, Squash, Leichtathletik (Weitsprung)	8
	Handball, Tennis, Basketball, Leichtathletik (laufen), Querfeldeinlauf / Eishockey, Fussball, Squash, Weitsprung, Querfeldeinlauf	7
	Badminton, Tennis, Basketball, Skifahren, Joggen bis 5x die Woche	6
	Radfahren, Skilanglauf / Joggen auf unebenem Boden mind. 2x/Woche / Schwerarbeit (Bauarbeiter)	5
	Skilanglauf, Radfahren, Joggen auf ebenem Boden mind. 2x die Woche / Zeitweise schwere Arbeit	4
	Schwimmen / Schwimmen / Leichte körperliche Arbeiten / Gehen auf unebenem Boden	3
	Kaum körperliche Arbeit / Gehen im Wald unmöglich	2
	Überwiegend sitzend / Gehen nur auf ebenem Boden möglich	1
	Arbeitsunfähigkeit aufgrund einer Knieverletzung / Normales Gehen nicht möglich	0

9.2.2.2 Assessment of Knee Stability

KT-1000 Arthrometer-, Lachman- and Pivot-shift testing are performed by the PI. All tests are performed first on the involved and secondly on the normal contralateral side.

KT-1000 Arthrometer testing is performed with the patient in supine position on a firm examination table. The knee is flexed to an angle between 20° and 35°. The thighs rest on a support platform. The KT-1000 Arthrometer testing device is then strapped to the anterior aspect of the tibia. After zeroing of the machine, tibial anterior displacement is measured. The measurement is performed once, and the results are noted in millimeters on the respective eCRF.

Lachman testing is performed by manual anterior displacement of the tibia in 15° flexion. The calf is grasped with one hand and quickly pulled anteriorly, while the other hand constrains the movement of the thigh. The test is performed once. The results are noted in the respective eCRF using the grading system displayed below.

Grade	Displacement
0	<3 mm
1	3 - 5 mm
2	>5 mm

For Pivot-shift testing, the anteriorly subluxated tibia head is repositioned manually. While a manual force is applied for internal rotation, valgisation and axial pressure, the knee is flexed manually from full extension. The rolling-gliding motion is assessed. The test is performed once. The results are noted in the respective eCRF using the grading system displayed below.

Grade	Finding
0	Normal
1	Glide
2	Clunk
3	Gross clunk with locking

9.2.3 Plain Radiography assessed Bone Tunnel Widening

BTW will additionally be assessed on plain radiograph. Bone tunnel width will be assessed at the widest part of the femoral bone tunnel. Bone tunnel width is defined as the largest distance between the opposing tunnel walls on a line orthogonal to the direction of the bone tunnel. Assessed will be the relative change in femoral bone tunnel width from baseline to respective follow-up.

9.2.4 Assessment of Other Outcomes of Interest

9.2.4.1 Clinical History

The following information regarding the clinical history of the patient will be gathered using eCRF:

- Date of the injury
- Affected side
- Activity at which injury occurred
- Mechanism of injury
- Comorbidities (if any)

9.2.4.2 Patient Demographics

The following information regarding patient demographics will be gathered using eCRF:

- Age
- Sex
- Height
- Weight
- Body Mass Index
- Smoking habit

9.2.4.3 Assessment during Surgery

The following information will be gathered at surgery:

- Date of surgery
- Comorbidities (if any) determined arthroscopically
- Additional surgical procedures (if any) not leading to patient exclusion (e.g. partial meniscectomy, meniscus repair)
- Side of autograft harvest (ipsilateral/contralateral)
- Tendon used (semitendinosus tendon with/without Gracilis tendon)
- Diameter of the femoral bone tunnel
- Diameter of the tibial bone tunnel
- Duration of the surgical procedure

9.2.5 Assessment of Safety Outcomes

9.2.5.1 Adverse Events

Intra-operative complications (if any) will be recorded on the eCRF. Self-reported AEs will be assessed by interviewing the patient. The following question will be used:
“Hatten Sie im Zusammenhang mit Ihrer Knieoperation irgendwelche nennenswerten medizinischen Probleme?”
Also any out of window visit or unexpected finding will be recorded. The following adverse event information will be recorded:

- Adverse event term
- Date of onset
- Date of resolution/Duration
- Severity (Subjective assessment by PI)
- Seriousness
- Relationship with surgical intervention
- Relationship with device under study
- Actions taken in response
- Outcome of the adverse event

9.2.6 Assessments in Participants Who Prematurely Stop the Study

Study subjects who withdraw consent to participate or who fail to appear to the scheduled visits will be contacted by telephone in order to obtain the interview for self-reported AEs.

9.3 Procedures at Each Visit

9.3.1 Screening (Visit 1)

Eligible patients will be informed about the ongoing study by the PI or by an involved practitioner, and will be handed out study patient information including informed consent form.

9.3.2 Baseline (Visit 2)

9.3.2.1 Admission Interview

Eligible Patients giving oral consent to study participation will be interviewed by the SN for detailed screening of inclusion/exclusion criteria. A patient information eCRF will be filled covering all necessary points for temporary admission of the patient into the study. Definite admission can only be acquired after the surgery. The signed informed consent form will be validated by signature by the PI and stored in the patient’s trial file. The patient will receive a copy of the signed informed consent form. For female patients of child bearing potential, a pregnancy test will be performed. The result of the pregnancy test will be photographed and the photograph will be signed by the PI and filed. The patient will be given the opportunity to clarify all uncertainties concerning the trial and the upcoming surgery with the PI. Also recorded will be the medical history and patient demographics. At this stage the preinjury activity level using Tegner activity scale will be assessed.

9.3.2.2 Preoperative Clinical Examination

Clinical examination will be conducted by the PI. The following information will be recorded in the eCRF:

- Date of examination.
- Intra/Extra-articular effusion.

- Knee mobility.
- Anterior displacement of the affected and of the healthy knee using the Lachman Test and the KT-1000 Arthrometer Test.
- Online survey for all patient-completed questionnaires (IKDC SKEF, LKSS and TAS)
- Rotational stability of both knees using the Pivot shift test.

9.3.2.3 Surgical Intervention

9.3.2.3.1 Surgery

See chapter 8.

9.3.2.3.2 Randomization

Patient randomization is acquired intraoperatively only if all inclusion criteria and no exclusion criteria have been met. The folded tendon-graft (not sutured, without OCS) must measure 8 – 8.5 mm in diameter at the end which is to be inserted into the femoral bone tunnel. If no intraoperatively assessed exclusion criteria are met (e.g. tendon-graft specifications, severe cartilage damage, extensive meniscus resection necessary) the subject is allocated to one of the two treatment groups. The envelope for the randomized group allocation of the subject is opened and the surgical procedure is carried out respectively. The envelope is sealed again afterwards and stored in the patient's trial file. The randomization procedure is described in detail in ACLROCS_WI_Randomization.

9.3.2.3.1 CT-Scan

The CT-scan will be performed according to ACLROCS_WI_CTScan.

9.3.2.3.2 Plain Radiography

Standard posteroanterior radiographs of the knee in full extension will be performed [ACLROCS_WI_PlainRadiography].

9.3.3 Follow-up 1 (Visit 3)

Follow-up 1 will be performed 42 days after surgery. The patient will be asked to fill an online survey for all patient-completed questionnaires (IKDC SKEF, LKSS and TAS) in the clinic. Subsequently, the clinical examination is conducted by the PI recording the identical points as during the preoperative clinical examination and the occurrence of any potential AEs. Plain radiography measurement is performed according to ACLROCS_WI_PlainRadiography.

9.3.4 Follow-up 2 (Visit 4)

Follow-up 2 will be performed equivalently to Follow-up 1. Additionally, CT-scanning is performed according to ACLROCS_WI_CTScan. This WI includes pregnancy testing and its validation by signature by the PI before the CT-scan. Follow-up 2 will be performed 4.5 months after surgery.

9.3.5 Follow-up 3 (Visit 5)

Follow-up 3 will be performed equivalently to Follow-up 2. It will be performed 1 year after surgery.

9.3.6 Follow-up 4 (Visit 6)

At Follow-up 4 patient-completed questionnaires and clinical examination will be performed equivalently to Follow-up 2 and 3. A plain radiography measurement (pregnancy test) will be done. No CT-scan will be performed. It is scheduled 2 years after surgery.

9.3.7 Follow-up 5 (Visit 7)

At Follow-up 5 no CT-scan and no plain radiography will be performed. Patient-completed questionnaires and clinical examination will be done equivalently to Follow-up 2 and 3. Additionally, the study-end eCRF will be filled-out. It is scheduled 5 years after surgery.

10 SAFETY

10.1 Medical Device Category A studies

10.1.1 Definition and Assessment of safety related events

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

Serious Adverse Event (SAE)
Adverse event that:

- results in death, or
- led to a serious deterioration in health that either:
  - results in a life-threatening illness or injury, or
  - results in a permanent impairment of a body structure or a body function, or
  - required in-patient or prolonged hospitalisation, or
  - results in medical or surgical intervention to prevent life threatening illness, or
- led to fetal distress, death or a congenital abnormality or birth defect. [ISO 14155: 3.37].

Health hazards that require measures
Findings that may require additional action are:

- Persistent anterior knee pain
- Septic arthritis
- Arthrofibrosis
- Graft rupture
- Aseptic effusion
- Subcutaneous cyst

10.1.2 Reporting of Safety related events

Reporting to Authorities:
In Category A studies it is the Investigator's responsibility to report to the local Ethics Committee

- **Health hazards** that require measures within 2 days

11 STATISTICAL METHODS

11.1 Hypothesis

Null hypothesis: Both treatments yield the same relative change in bone tunnel volume from baseline (Visit 2) to follow-up 3 (Visit 5).

$\mu_{Control} = \mu_{Intervention}$

Alternative hypothesis: The two treatments have a different effect on the primary endpoint after entire follow-up

$\mu_{Control} \neq \mu_{Intervention}$

11.2 Determination of Sample Size

For the power calculation a dedicated software (G*Power [84]) was used. It is aimed to detect a 20% difference in relative change of bone tunnel volume between the two groups. Pooling the standard deviations of the percentage volume change of different bone tunnel sections (articular/outside third) and two different tunnels (anteromedial/posterolateral tunnel) from the study conducted by Araki et al. [85] yields an estimate for the overall standard deviation of ±25.175%. With a type I error rate of α=0.05 and a power of 1-β = 0.8 and assuming both samples to be normally distributed and having equal variances, the required sample size per group is n = 25.
Accounting for a drop-out rate of 10% the total number of subjects for equally sized groups to be acquired is N = 56.

11.2.1 Power calculation of secondary outcome variables

Based on the calculated sample size above (expected drop-out excluded), power calculations for the secondary variables to be used for statistical inference testing are conducted. The table below shows the results of the power calculation of primary and secondary outcome variables.

	Tunnel Enlargement	IKDC Subjective Knee Evaluation Form	Lysholm Knee Scoring Scale	KT-1000 Arthrometer Test	Lachman Test	Pivot Shift Test
Test significance level, α	0.05	0.05	0.05	0.05	0.05	
Assumption of distribution	Normal	Normal	Normal	Non-normal	Non-normal	Non-normal
Difference in means to be detectable $\lvert\mu_{Control} - \mu_{Intervention}\rvert$	20% [86]	11.5 [87]	10 [88]	2 mm	0.5	0.8
Common standard deviation, σ	25.175% [85]	10 [86]	7 [86]	1.7 mm [86]	0.25	0.71 [86]
Effect size, $\delta = \lvert\mu_{Control} - \mu_{Intervention}\rvert / \sigma$	0.7944	1.15	1.429	0.88	2	1.13
Power	0.8	0.98	0.99	0.84	0.99	0.97
N per group (identically sized)	25	25	25	25	25	25

11.3 Statistical Criteria of Termination of Trial

Statistically significant inferiority (P ≤ 0.05) of the interventional treatment determined at 4.5 months follow-up on the primary efficacy outcome with a total of 20 patients (10 interventional, 10 control) will lead to premature termination of the study.

11.4 Planned Analyses

In all statistical analyses testing a significant difference in central tendency between the two groups, significance is set at α = 0.05. All statistical tests will be two-sided. The results of these tests will be reported in 95% confidence Interval and p-value for the Student's t-test and in Mann-Whitney U and p-value for the Mann-Whitney U test.

11.4.1 Datasets to be analyzed, analysis populations

Statistical analysis is based on the intention-to-treat analysis. In the case of the current trial this means that patients not following the rehabilitation protocol will not be excluded from analysis.

11.4.2 Primary Analysis

Confirmatory analysis is performed on the null hypothesis of equal relative changes in bone tunnel volume from baseline to last CT follow-up (follow-up 3, Visit 5) between the two groups. To make appropriate assumptions on the distribution of the data, the Kolmogorov-Smirnov Test is used to test for significant departure from normality. Significance is set at α = 0.05. In case the assumption of normality holds, a Student's t-test is performed to test for a significant difference in means between the two groups. In case the normality assumption is violated, a Mann-Whitney U test is applied. Mean values and standard deviations will be reported. The same procedure will be applied on the dataset of the first CT-follow-up (Visit 4) in the mode of a supportive analysis.

11.4.2.1 Confounder-Controlled Analysis

Additionally to the analysis described above in a secondary analysis, group differences in relative change of bone tunnel volume from baseline to follow-up 2 and from baseline to follow-up 3 are assessed in an analysis of covariance (ANCOVA)-model, controlling for confounding factors. The preliminary model contains the following confounding factors:

- Patient sex [89]
- Patient age [89]
- Preinjury Tegner activity score
- Associated bone/meniscus/cartilage-injury (Present/Not Present)

In a univariate analysis each factor is tested for association with the dependent variable (relative change of bone tunnel volume). All factors with association $p < 0.2$ are then included in a preliminary ANCOVA. A stepwise modelling approach is then used where variables with association $p > 0.05$ are excluded. At each exclusion, the model is computed again. The order of exclusion of all factors not associated significantly with the dependent variable is opposite to the list shown above (i.e. from bottom to top) [90].

11.4.2.2 Secondary Analyses

The procedures described hereafter will be applied on all follow-up datasets. Statistical significance testing is based on the Null hypothesis of both groups having an equal effect on the dependent variables.

11.4.2.3 Patient Subjective Knee Function

Mean values and standard deviations of the two groups at the different follow-up assessments will be reported. Due to the large number of distinct possible outcome values, the outcome of IKDC SKEF and LKSS are treated as continuous data [91]. Group means and standard deviations will be reported. If normal distribution can be assumed – tested with the Kolmogorov-Smirnov Test on an $\alpha = 0.05$ level - an independent-samples Student's t-test will be performed to detect significant differences between the group means. Otherwise – possibly due to a ceiling effect [87] - a Mann-Whitney U test is applied.

11.4.2.4 Assessment of Knee Stability

The side-to-side difference of the KT-1000 Arthrometer Test will be reported in group mean and standard deviation. The two group means will be compared with the Mann-Whitney U test.
The side-to-side difference [86] scores of the Lachman Test and the Pivot Shift Test will be reported in frequencies. Statistical inference testing will be done using the Mann-Whitney U test.

11.4.2.5 Tegner Activity Scale

The difference in TAS scores from baseline (pre-injury state) to follow-up will be reported in group mean and standard deviation. The two groups will be compared using the Mann-Whitney U test.

11.4.3 Other Outcomes of Interest

11.4.3.1 Intra-Patient Comparison of Ossification

The within-subject differences in femoral vs. tibial relative change in bone tunnel volume will be assessed for the interventional patient group. For descriptive statistics, mean and standard deviation values will be reported. For statistical inference testing, the null hypothesis in this setup is a mean difference in femoral vs. tibial relative change in bone tunnel volume equal to zero. If the normality assumption holds (Kolmogorov-Smirnov Test), a paired t test is applied to test for a significant two-sided departure from zero. Otherwise, a Wilcoxon signed-rank test will be used.

11.4.4 Plain Radiography assessed Bone Tunnel Widening

Radiographically assessed relative change of femoral bone tunnel width will be reported in group-mean values and in group standard deviation. Inter-group comparison will be performed using Student's t-test based on the relative change of femoral bone tunnel width at each assessed time point.

11.4.5 Interim analysis

An interim analysis will be conducted when the first 10 interventional patients have reached 4.5 months follow-up (Visit 4). All available data will be assessed, analyzed and evaluated equivalently to the full data analysis. To mitigate the risk for type II error, stopping criteria only include the primary outcome variable. Statistically significant ($P \leq 0.05$) inferiority of the interventional treatment in the primary outcome variable will lead to premature termination of the trial.

11.4.6 Safety Analysis

Safety will be evaluated by tabulations of AE's and SAE's and will be presented with descriptive statistics at baseline and follow-up visits for each treatment group. Inferential analyses of (serious) adverse events are not done.

11.4.7 Deviation(s) from the Original Statistical Plan

All deviations from the original statistical analysis plan will be provided in the final clinical study report.

11.5 Handling of Missing Data

Missing data will be left missing, i.e. no imputation scheme will be used. All data from a subject will be used for analysis, irrespective of possibly missing values.

11.6 Handling of Drop-Outs

Drop-outs are accounted for in the sample size calculation. Therefore no additional replacement of drop-out is planned.

12 DATA QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the investigation plan, ISO EN 14155, and applicable regulatory requirement(s).

Monitoring and Audits will be conducted during the course of the study for quality assurance purposes.

12.1 Data Handling and Record Keeping / Archiving

The study will strictly follow the investigation plan. If any changes become necessary, they must be laid down in an amendment to the investigation plan. All amendments of the investigation plan must be signed by the Sponsor-Investigator and submitted to CEC.

12.1.1 Case Report Forms

In the current study, eCRFs based on the data capture software REDCap [92] will be used. The software meets the requirements of good clinical practice. It is the responsibility of the PI to ensure correctness and completeness of the recorded data. After data recording, all data must be entered into eCRF as soon as possible. The name of the patient will not be visible in the eCRF. Personal data is encoded using a subject identifier. Study-related patient documentation and the signed informed consent form is to be stored in a patient specific folder. All data in the eCRF must be noted in the patient's medical file. All essential documents of the trial must be stored for a minimal duration of 15 years starting from study close-out. Patient's medical files must be stored for the maximum duration applicable at the clinic. The subject identifier key is stored in form of an enrolment-log on a different server than the eCRFs. Access is password restricted.

12.1.2 Specification of Source Documents

The following documents are considered source data, including but not limited to:

• SAE worksheets

• Nurse records, records of clinical coordinators, and

• Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if participant visited any during the study period and the post study period.

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) should be included in the source documents:

• Demographic data (age, sex)
• Inclusion and Exclusion Criteria details
• Participation in study and signed and dated Informed Consent Forms
• Visit dates
• Medical history and physical examination details
• Key efficacy and safety data (as specified in the investigation plan)
• AEs and concomitant medication
• Results of relevant examinations
• Laboratory printouts
• Dispensing and return of study device details
• Reason for premature discontinuation
• Randomization number

12.1.3 Record Keeping / Archiving

All essential documents of the clinical trial will be stored for a duration of at least 15 years. Patient medical files and other source data will be stored for the maximal time allowed by the University Hospital Balgrist. Printed patient medical files will be archived in an access restricted area. The patient medical file software (KISIM) and the study data capture software (REDCap) are access restricted.

12.2 Data Management

12.2.1 Data Management System, access and back-up

Subject-related data will be stored in the research electronic data capture software REDCap [92]. The PI is responsible for data recording. The PI will grant the relevant personnel user rights to view, edit or overwrite data entries by password as applicable. All edits will be automatically documented in the change history log.

12.2.2 Analysis and Archiving

For data analysis, subject-related data from REDCap will be exported and analyzed in statistics software (IBM - SPSS). Before data export, all patient identifiers will be removed. CT- and radiographic images will be analyzed using image analysis software (3D Slicer [83], MATLAB). All eCRF data will be stored for a minimum of 15 years in a safe storage facility at an external location. In-house archiving of research related data and responsibilities are outlined in the clinic's WI: UCAR_WI_013_Archiving_01.

12.3 Monitoring

Regular monitoring visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study.

All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for monitoring. The monitor will review all or a part of the eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.

A quality assurance audit/inspection of this study may be conducted by the competent authority or CEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

12.4 Confidentiality, Data Protection

Direct access to source data may be granted in the case of monitoring, audit or inspections. All personnel must treat patient data as confidential. As far as possible, encoded data will be used. Only persons listed on the staff list have access to the source data.

12.5 Storage of Related Health Data

All health-related patient data will be stored and archived in the data capture software REDCap. Patient-source data will be registered using subject identifiers. After full data analysis, all subject identifiers will be erased. Patient-source data may still be saved in the patient's medical record. Collection, disclosure, storage of patient-related data are carried out in accordance with Swiss data protection regulations and the Human Research Act. A requirement is the informed consent of every subject prior to inclusion in the clinical trial.

13 PUBLICATION AND DISSEMINATION POLICY

The sponsor-Investigator will make every effort to publish the data of the interim analysis, the primary endpoint analysis and the full data analysis in a peer-reviewed medical journal. No statistical codes or record IDs of study participants will be published. No trade secrets will be disclosed.

14 FUNDING AND SUPPORT

This study will mainly be financed by ZuriMED Technologies AG.

15 INSURANCE

The trial is covered by insurance by “Winterthur Versicherung” (Insurance number: 14.050.565). The insurance certificate is deposited at the cantonal ethics committee. For insurance coverage, patients must follow the instructions by the PI. The patient must report the occurrence of any health related complication to the PI. In such a case, as far as necessary, representatives of the insurance company may be granted access to the health-related patient data.

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17 APPENDICES

- Instructions for use SmartBone
- TechInfos SmartBone
- EC Certfificate SmartBone