PERFORMANCE AND SAFETY OF THE COMPOSITE INTERFERENCE SCREW USED IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTIONS

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PROTOCOL FOR RESEARCH INVOLVING HUMAN PARTICIPANTS

(Category 3 – Non interventional study)

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PROTOCOL AMENDMENT HISTORY

VERSION	DATE	DESCRIPTION OF THE MODIFICATION
N° 1.0	15/05/2019	First validated version presented to the Ethical Committee

VALIDATION AND SIGNATURES

SPONSOR	**BIOMATLANTE SA** **Julien DERT** CEO	In : _____ On : _____/_____/_____ Signature :
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LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
BPTB	Bone Patellar Tendon Bone
CFR	Code of Federal Regulations
CI	Confidence Interval
CIS	Composite Interference Screw
CPP	Committee for Protection of Persons
CRA	Clinical Research Associate
CRF	Case Report Form
DLSTG	Double-Loupe SemiTendinosus and Gracilis
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
KJ	Kenneth Jones
ICH GCP	International Conference on Harmonisation Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
PP	Per protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SS	Safety Set
ST4	SemiTendinosus
TEAE	Treatment-Emergent Adverse Events

SYNOPSIS OF THE STUDY

Title	Performance and safety of the Composite Interference Screw used in Anterior Cruciate Ligament Reconstructions
Sponsor	BIOMATLANTE SA
Coordinating investigator	Dr. Jaafar SBIHI
ANSM identification	2018-A03211-54
Justification / context	The evaluation of the clinical data has demonstrated the conformity of the Composite Interference Screw (CIS), with the relevant essential requirements for its use in orthopaedic applications. The Composite Interference Screws are intended for tibial and femoral ligament/graft fixation in the case of Anterior Cruciate Ligament (ACL) reconstructions. It has been concluded that the risks associated with the use of this medical device are acceptable when weighted against the benefits to the patients. In order to improve the clinical data on the CIS, the manufacturer, Biomatlante, decided to assess that the performance and safety of the device are maintained until the reaching of its intended use. In this objective, the goal of this study will be to observe the following parameters: 1. Objective IKDC score (clinical evaluation), 2. Subjective IKDC score (functional evaluation) 3. Safety (report of any adverse event) 4. Follow-up of the patient's recovery
Studied disease	Rupture of the Anterior Cruciate Ligament
Purpose of the device	☒ Treatment ☐ Screening ☐ Diagnostic ☐ Health services Research ☐ Supportive care ☐ Basic science ☐ Prevention ☐ Other
Study model	☒ Single group ☐ Crossover ☐ Parallel ☐ Factorial
Type of data	☐ Safety ☐ Bio-availability ☒Safety/Efficacy ☐ Pharmacokinetics ☐ Efficacy ☐ Pharmacokinetics/dynamics ☐ Bio-equivalence ☐ Pharmacodynamics
Number of arms	1
Medical device used	Osteotwin™ Composite Interference Screw (CE 0123)
Studied component	☐ Drug (including placebo) ☐ Biological / vaccine ☐ Radiation ☐ Genetic ☒ Device ☐ Procedure / surgery ☐ Behavioural ☐ Dietary supplement ☐ Other
Classification of the study	Category 3: Non-interventional study. This clinical investigation is prospective, monocentric and intra-subject comparative.

	The study is classified as category 3 according to the Jardé Law (French Law relative to the Clinical Research Involving Human Persons) and thus is qualified as "non-interventional". Indeed, according to the terms of the protocol established in collaboration with the stakeholders, this research will be carried out on a CE-marked device (CE 0123) and does not involve any risk or constraint since all the procedures will be performed and the products used in a usual way, without any additional or unusual diagnostic, treatment or monitoring action.
Intervention description	Fixation of a ligament/graft in a bone tunnel in order to reconstruct the damaged Anterior Cruciate Ligament.
Surgical technique	The surgical technique consists on the use of a tendon graft from the hamstring muscles: - DLSTG (Double-Louped SemiTendinosus and Gracilis) technique: use of tendon grafts from the Double-Louped SemiTendinosus and Gracilis muscles - ST4 (SemiTendinosus) technique: use of a tendon graft only from the SemiTendinosus muscle.
Primary endpoint measure	Evaluation of performance of the CIS in terms of ACL reconstruction by the clinical and functional evaluation of the knee.
Time points at which primary endpoint measure is assessed	- Pre-surgery (up to 4 months before surgery) - 7 months (± 1 month) post-surgery
Secondary endpoint measure	- Evaluation of safety of the CIS by the record of any adverse event during follow-up, especially the one mentioned in the Instructions For Use (IFU) - Follow-up of the patient's recovery by a visual clinical examination and the record of specific objective IKDC items
Time points at which the secondary endpoint measure is assessed	Safety data: From screening through visit at 7 months (± 1 month). Follow-up data: 2 months (± 2 weeks) post-surgery
Inclusion criteria	1. Acute or chronic ACL deficiency with complete or partial lesion of the anteromedial bundle requiring primary reconstruction of the ACL with hamstring tendons 2. Males or Females aged 18 to 60 years 3. No history of surgery on the affected knee 4. Patients not under guardianship or judicial protection 5. Signature of non opposition form (consent of the patient)
Exclusion criteria	1. History of ligament, meniscal surgery or fracture on the affected knee 2. Pregnancy or breastfeeding women
Study size	The sample size required for the study was determined in order to obtain sufficient final statistical power considering the 2 main criteria (co-primary endpoint). The statistical power used to determine the sample size required for each of the 2 main criteria is 90% to obtain a final statistical power of at least 80%.

	Subjective IKDC: The minimum relevant difference expected in the change at 7 months on the functional IKDC score is 11 points and the standard deviation expected in the IKDC score at both timepoint is 13 points. A total of 32 evaluable patients will be necessary to ensure a 90% power to detect a significant difference in the change at 7 months for two-sided test at the 5% level using paired Student t test or Wilcoxon test (depend of normality assumption). *Objective IKDC:* It is expected that 96% of patient will have modalities C or D before surgery [5]. Based on the investigator's experience, the proportion of total expected to shift from an IKDC modalities C or D to modalities A or B is 70% and proportion of total expected to shift from an IKDC modalities A or B to modalities C or D is 1%. A total of 11 evaluable patients will be necessary to ensure a 90% power to detect a significant difference for two-sided test at the 5% level using McNemar test. In order to ensure sufficient statistical power for both comparisons, the larger of the two required sample size is planned to be included, i.e. 32 patients. However, to increase the estimate precision of the co-primary endpoint, 50 completed patients will be targeted. With 50 patients, a precision around 13% can be achieved for the objective IKDC score and 3.6 points for the subjective IKDC score. This sample size will provide a final statistical power for primary objective of 97%. Accounting for a maximum of 10% dropouts or missing data, 56 patients should be recruited in the study.
Duration of the research	- Duration of the inclusion period: 12 months - Follow-up period per participant: maximum 12 months (at most 4 months before surgery and 8 months of follow-up) - Total research duration: 24 months
Statistical analysis of the data	A Statistical Analysis Plan (SAP) will be written by the Biostatistician and approved and signed by the Sponsor and the Coordinating Investigator before the first database lock. All data will be presented using descriptive statistics. An interim analysis is planned in this study protocol in order to obtain the preliminary results for first quarter 2020. Quantitative or ordinal variables will be described by the number of values entered, the number of missing data, the mean, the standard deviation, 95% confidence interval (CI) of the mean, the median, the 1st and 3rd quartiles, the minimum and the maximum. Qualitative variables will be described by the number of data filled in, the number of missing data, the frequency and the percentage of each modality. The 95% CIs of the percentages will be performed using exact confidence limits method. The medical and surgical histories and adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

	Primary efficacy endpoint The co-primary endpoint analysis will be performed on the Full Analysis Set (FAS) population. The scores recorded at 7 months (±1 month) after surgery will be compared to the scores recorded before surgery. The intra-subject comparison will be the main judgement criteria of success. The objective IKDC score will be dichotomised by combining modalities A and B and modalities C and D. The objective IKDC score at 7-months visit will be compared to the objective IKDC score before surgery using McNemar test or Q Cochrane test (if expected sample size for the contingence cell are less than 4). The subjective IKDC score at 7-months visit will be compared to the subjective IKDC score before surgery using paired Student t test or Wilcoxon test (depend of normality assumption). Sensitivity analyses using different analyses sets and missing data handling will be performed as described in section "Missing values / dropouts". The Per Protocol (PP) analysis will be considered as confirmatory analysis. **Secondary efficacy endpoint** The visual clinical examination and the record of specific IKDC items performed during the 2-months visit will be summarized using descriptive statistics on the FAS population. **Safety analysis** The safety analysis will be performed on the safety set (SS) population. Adverse Events (AEs) will be classified according to period of occurrence: pre-treatment AEs, Treatment-emergent Emergent AEs (TEAEs). TEAEs will be summarized and detailed by: • seriousness, • intensity, • action taken with trial medication, • other action taken, • relationship to study treatment, • severity according to the relationship with patient identifications The number/frequency of patients with each TEAE will be displayed by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA classification. All serious adverse events (SAEs) will be listed separately with the same information that the TEAE. All individual data will be presented in listings. The statistical analysis will be performed using SAS® or equivalent software. No sub-group analysis is planned.

Expected impacts	This study will confirm the ability of the CIS to help the reconstruction of Anterior Cruciate Ligament and its acceptable benefit/risk balance.
Keywords	Anterior cruciate ligament reconstruction, anterior cruciate ligament rupture, knee ligament reconstruction, knee ligament rupture

I. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

I.1. INTRODUCTION

ACL reconstruction with various strategies and therefore interference screws has become a routine surgery. Screws for ACL reconstruction provided by Biomatlante are widely used and their benefit/risk ratio has to be confirmed. Safety and performance of this CIS will be assessed in this study during a follow-up of 7 months (±1 month).

Moreover, any new information provided within this study may help improving the patients' health care undergoing ACL reconstruction with CIS.

I.2. CURRENT STATE OF KNOWLEDGE

From an anatomical point of view, the rupture of the Anterior Cruciate Ligament is characterized, at least in case of complete rupture, by their incapacity to heal spontaneously, whether or not there is immobilization of the knee. This disability is related to intra-articular Anterior Cruciate Ligament and vascular poverty of the ligament.

The diagnosis of rupture of the Anterior Cruciate Ligament is based on:

- The questioning: notion following a trauma of a crack or a disrobement;
- The clinical examination which is comparative and which seeks to highlight the laxity: Lachman's manipulation which objectifies anterior translation of the tibia under the femur at 20° of flexion, typically with a soft stop. This manipulation, always feasible even on a freshly traumatized knee, is of great specificity and sensitivity;
- Manoeuvring the jump, not feasible on an acute knee, but on a chronic laxity reproduces the sensation of instability felt by the patient;
- Anterior drawer at 90° which shows a globalization of laxity. Its absence does not mean an absence of ACL rupture [1].

In the absence of intervention, complete rupture of the Anterior Cruciate Ligament usually leaves a residual laxity.

Regardless of the patient's functional complaint, which is dominated by functional instability, rupture of the Anterior Cruciate Ligament is ultimately responsible for secondary meniscal lesions and osteoarthritis.

Ligament reconstruction of the Anterior Cruciate Ligament is a surgical technique that aims to meet two imperatives:

- Stabilize the knee and allow the patient to resume his activities, especially sports (functional result),
- Reserving the future of the knee by limiting the risk of secondary meniscal injury and possibly cartilaginous degradation [2].

Many techniques of reconstruction of the Anterior Cruciate Ligament (ACL) have been described in the scientific literature. One of the weak points of these reconstructions resides in graft fixation systems.

Since the 1990s, the use of patellar tendon plasty (with a bone bar) is emerging simultaneously with the appearance of titanium interference screws. Later, resorbable screws provide mechanical strength identical to metal screws but generate inflammatory reactions, a phenomenon described but not quantified in the literature. In order to overcome this phenomenon, screws made of PEEK (PolyEtherEtherKetone) make their appearances [3]. However, fixation with resorbable interference screws is recognized as gold standard for the fixation of the patellar tendon graft according to the Haute Autorité de Santé (HAS) in France [2].

One of the most used evaluation methods for assessment of patients' recovery after ACL reconstruction is the objective IKDC score (clinical evaluation) [4].

A review of the literature published on the known results of the subjective IKDC score (functional evaluation) makes it possible to estimate that the standard deviation around the mean will be about 13 points in post-operative condition:

Patients number	**Follow up**	**Mean or median**	**SD *or* *IQR/1.34***	**Reference**
134	6 months	84.5	12.1	(Ra 2014)
134	12 months	89.8	9.9	
28	pre-op	50.9	14.2	(Van de Graaf 2014)
43	5 months	59.8	20.2	
145	pre-op	39.9	18.1	(Ebrahimzadeh 2015)
1411	pre-op	*53*	*17.1*	(Cox 2014)
1308	2 years	*85*	*13.4*	
1307	6 years	*86*	*14.1*	
3741	0: subjects with no knee injury	91	12.8	(Anderson 2006)
4792	Unknown: Subjects with at least one knee problem (treated or not)	84	20.5	

In addition, articles (Cox 2014) and (Irrgang 2006) mention an IKDC threshold of 11 points to detect a clinically significant change, in a context of pre / postoperative comparison.

I.3. RESEARCH HYPOTHESES

The main objective of this study is to evaluate the performance of the Composite Interference Screw for ACL reconstruction with hamstring tendons in terms of objective (clinical evaluation) and subjective (functional evaluation) IKDC score. In the one hand, the hypothesis is at least 70% of the patients who will undergo ACL reconstruction with CIS will improve their objective IKDC from C or D to A or B (normal or almost normal) at 7 months (±1 month) post-surgery visit. In the other hand, our hypothesis is that the patients who will undergo ACL reconstruction with CIS will improve their subjective IKDC at least of 11 points at 7 months (±1 month) post-surgery visit.

I.4. JUSTIFICATION OF METHODOLOGICAL CHOICES

After patient information, objective and subjective IKDC scores will be collected before the operation and 7 months ±1 month after the operation and a clinical examination is scheduled 2 months ± 2 weeks after the operation.

All the examinations carried out are standard examinations, already integrated in the follow-up of the patients with lesion of the ACL according to the recommendations of good clinical practice.

The co-primary endpoint includes two main evaluation criteria to conclude on the efficacy of ACL reconstruction with CIS. The co-primary endpoint will be evaluated by objective and subjective IKDC scores recorded before surgery and at 7 months (±1 month) post-operative follow-up visit. The IKDC scores after surgery will be compared to the IKDC scores pre-surgery to determine the efficacy of the ligament/graft fixation by the screw.

I.5. EXPECTED IMPACTS

The study will confirm the performance and safety of the CIS in anterior cruciate ligament ruptures and its acceptable benefit/risk balance.

II. OBJECTIVES AND OUTCOMES

II.1. PRIMARY OBJECTIVE AND CO-PRIMARY ENDPOINT

The main objective of this study is to evaluate the performance of the Composite Interference Screw for ACL reconstruction at 7 months (±1 month) based on a co-primary endpoint including two main evaluation criteria:

- The objective IKDC score (clinical evaluation)
- The subjective IKDC (functional evaluation)

The co-primary endpoint will be recorded at two times:

- Before the operation (up to 4 months before surgery) (V-1)
- 7 months after the operation (±1 month) (V3)

The IKDC scores recorded at V3 will be compared to the scores recorded at V-1.

II.2. SECONDARY OBJECTIVES AND ENDPOINTS

The secondary objectives of this study are

- To evaluate the safety of the use of these screws by recording all adverse events that occurred during the study
- To follow the patient's recovery through a clinical examination at 2 months post-surgery (±2 weeks)

III. RESEARCH DESIGN

III.1. CLASSIFICATION OF THE STUDY

This clinical investigation is monocentric (Clinique Juge, Orthopedic Surgery Department), prospective, single arm and intra-subject comparative.

The study is classified as category 3 (non-interventional study) according to the Jardé law Law (French Law relative to the Clinical Research Involving Human Persons).

Indeed, according to the terms of the protocol established in collaboration with the stakeholders, this research will be carried out on a CE-marked device (CE 0123) and does not involve any risk or constraint since all the procedures will be performed and the products used in a usual way, without any additional or unusual diagnostic, treatment or monitoring action.

III.2. THE RESEARCH PROJECT AGENDA

- Duration of the inclusion period: 12 months.
- Duration of follow-up per participant: maximum 12 months (at most 4 months before surgery and 8 months of follow-up).
- Total duration of the research: 24 months.

III.3. SUMMARY TABLE OF THE PARTICIPANT FOLLOW-UP

	Before surgery V-1	Surgery V0	At discharge V1	At 2 months V2	At 7 months V3
	-4 months to Day 0	D0	D0	±2 weeks	±1 month
Full information and consent	X				
Inclusion / exclusion criteria	X	X			
Demographic data	X				
Patient information [a]	X				
Life habits [b]	X				
Relevant medical and surgical histories	X				
ACL RECONSTRUCTION					
Batch		X			
Medical device for femoral fixation		X			
Clinical indication		X			
PERFORMANCE					
Visual clinical examination[c]				X	
IKDC questionnaire - Subjective evaluation - Objective evaluation	 X X			 X [d]	 X X
SAFETY					
AEs	X<----------->X				

a. Patient information: height, weight, affected knee
b. Life habits: smoker, sport activities
c. Visual clinical evaluation: healing at the surgical site, walking test, quadriceps lock, articular amplitude (measured with a goniometer)
d. Evaluation of 2 items of the IKDC questionnaire at 2 months: Lachmann test and joint effusion items

III.4. INFORMATION OF THE PERSONS CONCERNED

During pre-inclusion visit, the Investigator (a qualified individual) will ask the participant and/or the legal guardians/legal representative to participate in the research project and provide him/her/them with information regarding:

- The objective of the study
- The automatic processing of participant-related data that will be collected during the research project, and shall also specify the participant's right to access, object to, or rectify the data.

The Investigator (a qualified individual) will also ensure that the eligibility criteria are met. If a person agrees to participate, he or she will give their consent orally. His or her non-opposition to data use will be recorded on a signed form and stored in his or her medical file. The participant may, at any moment, oppose the use of his or her data as part of the research.

III.5. FOLLOW-UP VISITS

- V -1, pre-inclusion visit: -4 months to Day 0 (before surgery)
  - Check of inclusion/exclusion criteria
  - Patient Information: weight, height, affected knee (right, left)
  - Demographic data: Age, sex
  - Life habits: smoker, sport activities
  - Relevant medical and surgical histories
  - IKDC questionnaires (objective and subjective dimension)
  - Signature of the written consent

- V 0, inclusion visit: surgery
  - Check of inclusion/exclusion criteria
  - Batch number of CIS medical device
  - Medical device used for femoral fixation
  - Clinical indication (Double-Louped SemiTendinosus and Gracilis tendon (DLSTG), SemiTendinosus tendon (ST4) or Bone-Patellar Tendon-Bone (BPTB also called Kenneth Jones method)
  - AEs report

- V 1, follow-up visit: at discharge
  - AEs report

- V 2, follow-up visit: at 2 months (±2 weeks)
  - Visual clinical examination: healing, walking test, quadriceps lock and articular amplitude
  - Several items of the objective IKDC questionnaire (Lachmann test and joint effusion items)
  - AEs report

III.6. END OF RESEARCH VISIT

- V 3, follow-up visit: at 7 months (±1 month)
  - IKDC questionnaires (objective and subjective dimension)
  - AEs report

IV. STUDY POPULATION

IV.1. INCLUSION CRITERIA

1. Acute or chronic ACL deficiency with complete or partial lesion of the anteromedial bundle requiring primary reconstruction of the ACL with hamstring tendons
2. Males or Females aged 18 to 60 years
3. No history of surgery on the affected knee
4. Patients not under guardianship or judicial protection
5. Signature of non opposition form (consent of the patient)

IV.2. EXCLUSION CRITERIA

1. History of ligament, meniscal surgery or fracture on the affected knee
2. Pregnancy or breastfeeding women

IV.3. FEASIBILITY AND RECRUITMENT PROCEDURES

The study will be conducted at the Clinique Juge Orthopedic Surgery Department in association with Dr Jaafar SBIHI. The service already has a systematic and standardized follow-up of the patient with an ACL lesion developed according to the recommendations in good clinical practice.

The site is currently doing more than 100 ACL reconstructions a year. The service will recruit a maximum of 56 patients. All patients recruited will be patients requiring ACL reconstruction and who will receive the Composite Interference Screw manufactured by Biomatlante. The indication of treatment (surgical or not) will not be influenced by the study and will be performed according to good clinical practice.

The inclusion of patients is scheduled for a maximum of 12 months.

Patients fulfilling the study criteria will be offered to participate in the study. Those who accept will be assigned an identification number. This number will be re-used on all documents related to the study in order to preserve the patient's anonymity on these documents.

IV.4. ACTIONS UPON PATIENT WITHDRAWAL

If a patient withdraws prematurely from the study, study personnel should make every effort to complete the full panel of assessments scheduled until the 7-months visit. The reason for patient withdrawal must be documented in the electronic Case Report Form (eCRF).

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, which indicates to the Investigator that continued participation, is not in the best interest of the patient;
- Pregnancy;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records. Withdrawn patients will not be replaced.

V. TREATMENT/ STRATEGY(IES)/ PROCEDURE(S) OF THE RESEARCH

V.1. DESCRIPTION OF SURGICAL TREATMENT FOR ACL RECONSTRUCTION (HAS RECOMMENDATIONS)

Intra-articular ligamentoplasty technique:

Ligamentoplasty is preferentially performed by arthroscopy taking into account the complete assessment of the articulation that it allows in the same operating greater rapidity of operative follow-up, decrease in morbidity, speed of recovery.

Which transplant?

- No prospective comparative study concludes on the use of the quadricipital tendon or fascia lata.
- Overall subjective and objective results are identical with transplant Bone-Patellar Tendon-Bone (BPTB technique also called Kenneth Jones technique) or the transplant using the Double-Louped SemiTendinosus and Gracilis tendon (DLSTG technique).
- The anterior pains (of tendinous or neuropathic origin) and the flessum are more frequent with the BPTB than with the DLSTG but the impact on the level of sports recovery is equivalent between the two techniques. Previous pain can, however, have a professional impact (an activity requiring kneeling).

What fixation?

Patellar Bone-Tendon Bone (BPTB technique also called Kenneth Jones technique):

- The fixation with a femoral interference screw and a tibial interference screw is the reference technique.
- Double fixation to the femur or tibia is useless unless the screw is held poorly interference (especially in the tibia).
- The screw can be metallic or bioresorbable.
- The bioresorbable screw has the advantage of facilitating the reading of a possible postoperative MRI and possible surgical revision.

Double-Louped SemiTendinous and Gracilis tendon (DLSTG technique):

- In the femur, it can use an extra-anatomic system, an interference screw or any other intraductal system. To date, no study recommends a double femoral fixation.
- In the tibia, the traction is in the axis of the transplant. This can lead to propose, especially when the bone behaviour is poor, a double fixation or strengthened.

Lateral tenodesis:

- Regardless of age, isolated lateral tenodesis is not recommended.
- There is no indication to perform systematic associated lateral tenodesis, in front of chronic anterior laxity.
- Lateral tenodesis associated with intra-articular reconstruction cannot be considered only in the context of an overall previous laxity.

V.2. DESCRIPTION OF THE PRODUCT

The Composite Interference Screw (CIS) manufactured by Biomatlante is sterile, resorbable and osteoconductive of synthetic origin. The Composite Interference Screw is in the form of a cannulated screw:

Figure 1: Composite Interference Screw

The Composite Interference Screws are available in different diameters (from 7 to 12 mm), and several different lengths depending on the diameters (from 20 to 35 mm). Different diameters and lengths of implants are available to allow adaptation to the bone site but also to the patient's anatomy.

The design is suitable for easy installation, without tissue damage (self-tapping thread and atraumatic head).

These resorbable fixation systems are intended to be fully absorbed by the body during the process of bone healing.

They consist of:

- a polymer: poly (L-lactic-co-D, L-lactic acid) (PLDLLA)
- calcium phosphate granules (Hydrodyapatite and Bêta Tricalcium Phosphate)

The polymer / granule ratio of calcium phosphate used here is 75% / 25%.

V.3. INTENDED USE

The Composite Interference Screw is intended to be used for knee ligament reconstructions.
The claimed performance for the Composite Interference Screw is as follows: fixation of the ligament/graft within the bone tunnel until bone consolidation is complete.

V.4. SURGICAL INDICATION

The Composite Interference Screw is indicated for torn ligaments in the knee.
The Composite Interference Screw is reserved exclusively for adults. The material has not been tested on pregnant or breastfeeding women.

V.5. CHOICE OF TREATMENT IN THE STUDY

Recruited patients will have an indication of ACL reconstruction with a tendon graft from hamstring muscles:

- DLSTG (Double-Louped SemiTendinosus and Gracilis) technique: use of tendon grafts from the Double-Louped SemiTendinosus and Gracilis muscles
- ST4 (SemiTendinous) technique: use of a tendon graft only from the SemiTendinosus muscle.

In the femur, the fixation will be assured by an intraductal system (Endobutton) and the composite interference screw will be used for the tibial fixation only. The indication of treatment (surgical or otherwise) after ACL injury will not be influenced by the study and will be performed according to good clinical practice.

Patients for whom a patellar tendon (BPTB technique also called Kenneth Jones technique) is advised by the surgeon according to good clinical practice will not be included.

During this study, the investigators' practices will not be modified. For each type of surgery, the surgeon will perform all his acts in accordance with his current practice, without adding any additional procedure.

The Composite Interference Screw should be handled in accordance with the manufacturer's recommendation using sterile instruments.

V.6. CONTRAINDICATIONS

- Acute infections
- Known allergies to the material (if an allergy of any type is suspected, the appropriate examinations must be carried out beforehand)
- Fever and/or local inflammation
- Mediocre or insufficient bone quality (especially in the event of tumours and severe osteoporosis).
- Limited blood flow at the graft site (necrosis, prior infections)

V.7. AUTHORIZED OF FORBIDDEN TREATMENTS AND PROCEDURES

No prior or concomitant medication will be prohibited.

VI. STUDY ASSESSMENT AND PROCEDURES

VI.1. MAIN EVALUATION CRITERION

For assessment of CIS performance in ACL reconstruction, the investigator will evaluate the objective IKDC score and the patient will evaluate the subjective IKDC score:

- Before the operation (up to 4 months before surgery)
- 7 months after the operation (±1 month)

The objective IKDC exam is a classic manual examination of the surgeon during the diagnosis and follow-up of the patient and does not involve any risk for the patient. Four level are used in objective IKDC evaluation coded from A to D (A: Normal, B: Almost normal, C: Abnormal and D: Very abnormal). The first three item groups (joint effusion, loss of passive mobility and ligament assessment) will be used to determine the objective IKDC score. The item group with the lowest level determines the final evaluation for the objective IKDC evaluation. The item groups from 4 to 7 are not required for the determination of the objective IKDC score; the completion of these item groups is optional. In this study, only the first three items groups will be completed.

The subjective IKDC questionnaire provides an overall functional score. The questionnaire looks at 3 categories: symptoms, sports activity, and knee function. The symptoms subscale helps to evaluate things such as pain, stiffness, swelling and giving-way of the knee. Scores are obtained by summing the individual items, then transforming the crude total to a scaled number that ranges from 0 to 100. This final number is interpreted as a measure of function with higher scores representing higher levels of function.

VI.2. SECONDARY EVALUATION CRITERIA

Safety assessment of CIS in ACL reconstruction, the investigator will report all Adverse Events (AEs)

The clinical examination performed during the 2-months visit allows the surgeon to follow the patient's recovery. The parameters collected during this visit are as follows:

- Visual clinical examination:
  - Healing at the surgical site: total healing, partial healing and no healing.
  - Walking test: the patient always uses these crutches (yes/no).
  - Quadriceps lock: when the leg is extended, if the kneecap rises, the patient has locked his quadriceps properly and we have a recovery of the quadriceps function. The answer will be yes/no.
  - Articular amplitude: the test is carried out using a goniometer to measure the flexion angle and the extension angle. The values in degrees will be recorded both in flexion and extension.

- Objective IKDC items:
  - Lachman test: the Lachman test will be performed manually. This test is a passive accessory movement test of the knee performed to identify the integrity of the anterior cruciate ligament (ACL) and is designed to assess single and sagittal plane instability.
  - Joint effusion: the joint effusion is determined by palpation of the knee.

VI.3. MANAGEMENT OF ADVERSE EVENTS

The investigator records the adverse events or an abnormal analysis result defined in the protocol as determinants for the safety assessment, keeps a documentary record and notifies the sponsor.

The investigator informs the sponsor of all adverse events that occurred in the participants.

VI.3.1. DEFINITION OF ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a medical device, which does not necessarily have a causal relationship with this device. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the eCRF.

Adverse events will be monitored and documented from the time of informed consent to the end of study participation. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with the signing of informed consent, investigators should make an assessment for adverse events at each visit and record the event on the adverse event section of the eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, transfusion) should be recorded as an adverse event.

Any medical condition already present at the time of screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

VI.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death: AE causes or contributes to the death;
- A life-threatening adverse event: AE places the subject at immediate risk of death; it does not refer to AE which hypothetically might have caused death if it were more severe;
- Requires hospitalization or prolongation of existing hospitalizations: AE requires at least an overnight admission or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (i.e. plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion;
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event: AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

VI.3.3. CLASSIFICATION OF AN ADVERSE EVENT

VI.3.3.1. Severity of event

The severity of AEs must be assessed by the Investigator according to the following definitions. The term “severity” is used to describe the intensity of a specific event. This has to be distinguished from the term “serious”.

- Mild: Events require minimal or no treatment and do not interfere with the participant’s daily activities
- Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

VI.3.3.2. Relationship to study product

The clinician must always determine the relationship between all adverse events and the investigated medical device by the examination and evaluation of the participant on the basis of temporal relationship between the AE and application of the device and his/her clinical judgment. In a clinical trial, the investigated medical device must always be suspected. The degree of certainty about causality will be graded using the categories below:

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician

VI.3.3.3. Expected adverse events

The most frequent adverse events expected from Composite Interference Screw observed in patients are:

- Postoperative infection
- Irritation
- Allergy
- Reduced patient mobility
- Pain
- Fever
- Inflammatory reaction

Certain adverse events can be treated with medicines or may require additional surgery.

VI.3.4. ADVERSE EVENTS REPORTING

Complete and accurate data on all AEs experienced for the duration of the reporting period, will be reported in the eCRF.

It is important that each AE report includes a description of the event, whether it is considered serious, its duration (onset and resolution dates), its severity, its relationship to the investigational product, any other potential causality factors, any treatment given or other action taken and its outcome.

As defined in Article R5212-17 of the French Public Health Code, all incident or risk of incident resulting from the use of a medical device brought to the investigator's attention will be the subject of a spontaneous report from the investigator to the local vigilance correspondent on whom he depends or, failing that, to the French National Agency for the Safety of Health Products (Agence Nationale de Sécurité et du Médicament : ANSM) in accordance with the usual procedures in force.

These declarations should be addressed at:

Direction de la surveillance – Plateforme de réception et d'orientation des signalements

E-mail: materiovigilance@ansm.sante.fr

Fax: 01.55.87.37.01

All AEs occurring from the time of informed consent until end of study participation must also be reported to the sponsor.

All AEs that the Investigator considers related to the medical device occurring after the end of study participation must be reported to the sponsor.

To report the AE, the AE form can be filled. When the form is completed, signed and dated, it must be sent to the sponsor, specifically to the vigilance contact:

Vigilance contact :
Nancy TRICHEREAU
Quality Assurance Manager
E-mail: materiovigilance@biomatlante.com
Phone: 06.21.90.58.43

Immediately after receiving the follow-up information, the Investigator must update the AE form and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to the sponsor.

For any research involving the human, where an unexpected serious adverse reaction or a new fact relevant to the research or product under investigation is likely to prejudice to the safety of the appropriate persons, the proponent and the investigator shall take appropriate urgent safety measures.

VI.3.5. NEW FACTS REPORTING

A new fact is defined as any new safety data which may lead to a reassessment of the relationship between the benefits and risks balance of the research or the product being investigated, changes in the use of the product, the conduct of the research or documents relating to the search, or to suspend or interrupt or modify the protocol of the search or similar searches. (R.1123-46 of the French Public Health Code).

In the case of a new medical fact, the Sponsor, will be responsible for reporting new facts to the authorities in accordance with national regulations, as follows:

- Inform without delay the ANSM about the new medical fact, at the following email address: aec-essaiscliniques@ansm.sante.fr with the following subject: Fait nouveau / trial number/ international non-proprietary name (INN) or substance code and including:
  - ID-RCB N°,
  - Title of the study protocol,
  - Protocol code number,
  - Summary of the new fact and urgent safety measures implemented if necessary,
  - All relevant information for the evaluation of the new fact.
- Inform without delay the director of the Agence Régionale de Santé (ARS; regional health agency) and the Ethics Committee (CPP).

Any follow-up information with regards to the new safety medical fact will be reported to the regulatory authorities within 8 calendar days, and details regarding the urgent safety measures set up will be sent within 15 days to the regulatory authorities.

VII. STATISTICAL ASPECTS

VII.1. SAMPLE SIZE DETERMINATION

The sample size required for the study was determined in order to obtain sufficient final statistical power considering the 2 main criteria (co-primary endpoint). The statistical power used to determine the sample size required for each of the 2 main criteria is 90% to obtain a final statistical power of at least 80%.

Subjective IKDC:

The minimum relevant difference expected in the change at 7 months on the functional IKDC score is 11 points and the standard deviation expected in the IKDC score at pre-surgery and at 7 months is 13 points. A total of 32 evaluable patients will be necessary to ensure a 90% power to detect a significant difference in the change at 7 months for two-sided test at the 5% level using paired Student t test.

Objective IKDC:

It is expected that 96% of patient will have modalities C or D before surgery [5]. Based on the investigator's experience, the proportion of total expected to shift from an IKDC modalities C or D to modalities A or B is 70% and proportion of total expected to shift from an IKDC modalities A or B to modalities C or D is 1%. A total of 11 evaluable patients will be necessary to ensure a 90% power to detect a significant difference for two-sided test at the 5% level using McNemar test.

In order to ensure sufficient statistical power for both comparisons, the larger of the two required sample size is planned to be included, i.e. 32 patients.

However, to increase the estimate precision of the co-primary endpoint, 50 completed patients will be targeted. With 50 patients, a precision around 13% can be achieved for the objective IKDC score and 3.6 points for the subjective IKDC score. This sample size will provide a final statistical power for primary objective of 97%.

Accounting for a maximum of 10% dropouts or missing data, 56 patients should be recruited in the study.

VII.2. ANALYSIS SETS

Four populations will be defined:

- Screened population will include all patients entering the study,
- Safety Set (SS) population will include all patients who received the surgical intervention,
- Full Analysis Set (FAS) population will be defined by all patient who received the CIS product and in whom at least one efficacy information has been collected after the application of the CIS,

- Per-Protocol (PP) efficacy population will include all patients in FAS population without any major protocol deviation.

Remark: according to the ICH E9 recommendations, this subset of patients corresponds to a subset of the full "intention-to-treat" analysis set, being the Full Analysis Set (FAS).

VII.3. MISSING VALUES AND DROP-OUT

For the primary analysis (FAS analysis), in the case of a patient with missing data, the corresponding data will not be replaced.

For sensitivity analyses, some of the missing data may be replaced. It will be performed according to the following scenarios:

- Best-worst scenario: the missing data on the pre-surgery objective IKDC score will be considered with an objective IKDC score to A and missing data on the 7-months objective IKDC score will be considered with an objective IKDC score to D.
- Worst-best scenario: the missing data on the pre-surgery objective IKDC score will be considered with an objective IKDC score to D and missing data on the 7-month objective IKDC score will be considered with an objective IKDC score to A.
- Last Observation Carry Forward (LOCF) method: the missing data on the 7-months subjective IKDC will be replaced using LOCF method.

No other missing data will be replaced.

VII.4. STATISTICAL ANALYSIS

VII.4.1. GENERAL CONSIDERATION

A Statistical Analysis Plan (SAP) will be written by the biostatistician detailing the statistical analysis. This document will be approved and signed by the Sponsor and the Coordinating Investigator before the first database lock.

The statistical analysis will be performed on SAS® version 9.4 or later (or equivalent statistical software).

- *Descriptive statistics*

Quantitative variables will be described by the number of values entered, the number of missing data, the mean, the standard deviation, the 95% CIs for the means, the median, the 1st and 3rd quartiles, the minimum and maximum.

Qualitative variables will be described by the number of data filled in, the number of missing data, the frequency and the percentage of each modality. The 95% CIs of the percentages will be performed using exact confidence limits method.

All variable in the database will be described using descriptive statistics and all individual data will be presented in listings.

- *Inferential test*

All tests will be two-sided and the type I error (α) will be set at 5%.

Quantitative score at 7-months visit will be compared to the score before surgery using paired Student t test or Wilcoxon test (depend of normality assumption).

Qualitative score at 7-months visit will be compared to the score before surgery using McNemar test or Q Cochrane test (if expected sample size for the contingence cell are less than 4).

One interim analysis and no sub-group analysis will be planned.

- *Pre-analysis review of patient data*

Following the ICH guideline E9, a data review meeting will be held before the final database locking. The following items will be discussed:

- By-patient, list of protocol violations and other issues with the data, and definition of the analysis sets,
- Need for amendment to the SAP, based on newly gained research information and on the examination of the data.

If required, the SAP will be amended. Data discrepancies detected at the pre-analysis data review meeting will be resolved. Subsequently, the database will be locked, and the analyses will be performed.

- *Protocol deviations*

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or manufacturer recommendation requirements. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site investigator to use continuous vigilance to identify deviations. All deviations must be reported in study source documents.

All protocol deviations will be listed before the data review meeting and reviewed during this meeting and classified as “minor” or “major".

Number and frequency of patients with protocol deviations will be tabulated.

Patients presenting major deviation will be excluded from the PP efficacy population and therefore will not be taken into account on the primary efficacy analysis in the PP population.

VII.4.2. ANALYSIS OF THE CO-PRIMARY EFFICACY ENDPOINT

According to the Food and Drug Administration (FDA) guidance for industry – Multiple endpoints in clinical trials and European Medicines Agency (EMA) Guideline on multiplicity issues in clinical trials, for conclude that the CIS is effective, it will be necessary to demonstrate an effect on each of the primary endpoints. However, there is only one result that is considered a study success, namely, that all of the separate endpoints are statistically significant. Testing all of the individual endpoints at the 0.05 level does not cause inflation of the Type I error rate; rather, the impact of co-primary endpoint testing is to increase the type II error rate.

The co-primary endpoint analysis will be performed on FAS population.

The scores recorded at 7 months (±1 month) after surgery will be compared to the scores recorded before surgery. The intra-subject comparison will be the main judgement criteria of success.

The objective IKDC score will be dichotomised by combining modalities A and B and modalities C and D.

The objective IKDC score at 7-months visit will be compared to the objective IKDC score before surgery using McNemar test or Q Cochrane test (if expected sample size for the contingence cell are less than 4).

The subjective IKDC score at 7-months visit will be compared to the subjective IKDC score before surgery using paired Student test or Wilcoxon test (depend of normality assumption).

Sensitivity analyses using different analyses sets and missing data handling as described above will be performed as described in section “Missing values / dropouts”. The PP analysis will be considered as confirmatory analysis.

VII.4.3. ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT

The visual clinical examination and the record of specific IKDC items performed during the 2-months visit will be summarized using descriptive statistics on the FAS population.

VII.4.4. SAFETY ANALYSIS

The safety analysis will be performed on SS population.

Safety endpoints will be AEs and SAEs all through the study.

AEs will be coded using last version available of the Medical Dictionary for Regulatory Activities dictionary (MedDRA). AEs will be classified according to period of occurrence: pre-treatment AEs and Treatment-Emergent AEs.

- Pre-treatment AEs are defined as adverse events occurring before the introduction of the investigational product.
- Treatment-Emergent AEs (TEAEs) are defined as an adverse who that emerges after introduction of the investigational product having been absent pre-treatment, or worsens relative to the pre-treatment state.

AE reporting will focus on TEAEs. TEAEs will be summarized and detailed using descriptive statistics by:

- seriousness,
- intensity,
- action taken with investigational product,
- other action taken,
- relationship to study treatment,
- severity according to the relationship with patient identifications.

The number and frequency of patients with each TEAE will be displayed by System Organ Class and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) classification.

All SAEs will be listed separately with the same information that the TEAE.

VII.4.5. BASELINE DESCRIPTIVE STATISTICS

The baseline value will be defined by the last measured value before the ACL surgery.

Descriptive statistics of demographics and other baseline characteristics will be presented on the FAS population.

Medical history will be summarized for all included patients on the FAS population. Frequency of pathologies will be summarized using descriptive statistics. Frequency will be given by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA).

Prior and concomitant medications will be summarized for all included patients on the FAS population.

Prior and concomitant medications coded using the ATC classification system will be tabulated by anatomical main group, therapeutic/pharmacological subgroup and by chemical substance. Prior medications will be defined as medications used by subjects in the 3 months prior to screening visit and stopped before surgery.

VII.4.6. PLANNED INTERIM ANALYSES

One interim analysis is planned in this study protocol during the first quarter of 2020.

This analysis will be carried out using only descriptive statistics. No p-value will be generated in order to prevent the alpha inflation for the final analysis.

VII.4.7. SUB-GROUP ANALYSES

No sub-group analysis is planned.

VII.4.8. TABULATION OF INDIVIDUAL PATIENT DATA

All individual data will be presented in the listing table in accordance with the guidance ICH E3.

VIII. RIGHTS OF ACCESS TO DATA AND SOURCE DOCUMENTS

BIOMATLANTE, sponsor of the research, is identified as the data processing controller. As a result, it must be in compliance and ensure that the data will be processed by the various research actors, in accordance with Law 78-17 of 6th January 1978 amended by Law 2014-344 of 17th March 2017, known as "Informatique et Libertés", and the European Regulation 2016/679 of 27th April 2016 (known as "GDPR").

VIII.1. ACCESS TO DATA

Agreement to participate in the protocol means that the individuals carrying out the research will make documents and individual data that are strictly necessary to follow-up, quality control and audit available to the individuals who have a right to access these documents in accordance with applicable legal and regulatory provisions.

VIII.2. SOURCE DATA

This includes all information contained in the original documents, or in authenticated copies of these documents, relating to clinical examinations, findings or other activities carried out as part of the research and necessary to the reconstitution and evaluation of the research. The documents in which source data are recorded are called source documents.

The source document to be used will be:

- Medical patient file
- Patient questionnaires

VIII.3. DATA CONFIDENTIALITY

In accordance with applicable legal provisions, individuals who have direct access to source data take all the necessary precautions to ensure the confidentiality of information relating to research, participants and particularly their identity, as well as the results obtained. These individuals, like the investigator and the person who performs data monitoring, are subject to the conditions of professional secrecy.

During the research project or at the end of it, the collected data on participants and data transmitted to the sponsor by the investigator (or any other involved specialists) will be codified. The data must not, under any circumstances, clearly indicate the names of the participants or their address.

Only the first letter of the name and surname of the subject will be recorded, together with a research-specific coded number indicating the order of inclusion of the subjects for each center.
The sponsor will ensure that each participant of the research project will be informed about access to data relating to him or her and strictly necessary for quality control.

VIII.4. PSEUDONYMIZATION PROCEDURE

In the context of this study, the personal data of patients will be processed in order to meet the research objectives.
For this purpose, patient's medical data will be transmitted to the sponsor. For each patient, these data will be identified by the number attributed to the research center and the identification number of the patient.

The number attributed to the research center is attributed as follows:
Clinical center N°01 : Clinique Juge, Orthopedic Surgery Department - Dr Jaafar SBIHI

The patient identification number is attributed as follows:

- Number corresponding to the order of inclusion in the research center
- First letter of the patient's first name
- First letter of the patient's name

Center N°: ‖_0 1_‖
Patient N°: ‖_0_‖_1_‖_X_‖_X_‖ **Inclusion N°**
Investigator : _____

Only the investigator, its collaborators and the person responsible for the quality control of the data will have access to directly identifying data (name, date of birth, etc) via the correspondence table.

IX. QUALITY CONTROL AND QUALITY ASSURANCE

IX.1. GUIDELINES FOR COLLECTING DATA

All the information required by the protocol must be recorded in case report forms and an explanation must be provided for any missing data.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form derived from source documents should be consistent with the data recorded on the source documents. Clinical data will be entered directly from the source documents.

IX.2. RESEARCH FOLLOW-UP

The Clinical Research Associate (CRA) will ensure research follow-up and will be responsible, under the Coordinating Investigator, for:

- Logistics and the monitoring of research,
- Reporting on the study's progress,
- Verifying that the case report form is updated (request for additional information, corrections, etc.),
- Sending samples.

The CRA will work in accordance with standard operating procedures, in collaboration with the research associate delegated by the sponsor.

IX.3. QUALITY ASSURANCE AND QUALITY CONTROL

A CRA will visit each center, during the implementation of the research, once or several times during the course of the research project, according to the monitoring plan defined for the research and the frequency of inclusions. The elements to be reviewed during these visits are defined by the monitoring plan. All visits will be subject to a written monitoring report. The sponsor will be in charge of the quality survey of the study.

Following written monitoring plan, the clinical research associate will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Manufacturing Practices).
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

IX.4. DATA MANAGEMENT

IX.4.1. DATA HANDLING

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

IX.4.2. COMPUTER SYSTEMS

Data will be processed using a validated computer system conforming to regulatory requirements.

IX.4.3. DATA ENTRY

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

IX.4.4. MEDICAL INFORMATION CODING

For medical information, the latest version at the time of study start of the Medical Dictionary for Regulatory Activities (MedDRA) for medical history and adverse events will be used.

IX.4.5. DATA VALIDATION

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs panel for each patient will be electronically signed by the Investigator.

IX.5. PROTOCOL DEVIATION

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or manufacturer recommendation requirements. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site investigator to use continuous vigilance to identify deviations. All deviations must be reported in study source documents.

Examples of protocol deviations are presented below (non-exhaustive list):

- The screw has not been installed,
- Violation of inclusion/non-inclusion criteria,
- Post-inclusion protocol violation,
- Non compliance with visit scheduled

All protocol deviation will be listed before the data review meeting and reviewed during this meeting and classified as “minor” or “major".

Number and frequency of patients with protocol deviations will be tabulated.

IX.6. AUDIT AND INSPECTION

Individuals appointed by the sponsor and independent of those conducting the study may carry out audits at any moment. The audit is designed to check the safety of the participants and the respect of their rights, compliance with applicable regulations and data reliability.
An inspection may also be undertaken by a competent authority (ANSM in France or EMA within the framework of a European study, for example).
The audit, as well as the inspection, may be applied to any stage of the research, from protocol development to the publication of results and the classification of data used or produced as part of the research project.
The investigators shall comply with the sponsor’s requirements regarding the audit and the competent authority’s inspection of the research.

X. ETHICAL AND REGULATORY CONSIDERATIONS

X.1. COMPLIANCE WITH REFERENCE TEXTS

The sponsor and the person(s) who directs(s) and supervise(s) the research commit themselves to ensure that this research is carried out in accordance with the law no. 2012-300 of 5 March 2012 on research involving the human person and the Declaration of Helsinki (which can be found in full at http://www.wma.net/en/30publications/10policies/b3/).

This research project will receive the positive endorsement of the CPP (Committee for the Protection of Persons – French equivalent of an Ethical Committee) and will be reported to the ANSM (the French National Agency for the Safety of Health Products).The data recorded during this research are the subject of a computerised processing at ATLANSTAT in accordance with the law no. 78-17 of 6 January 1978 on data processing, files and freedom as amended by Law 2004-801 of 6 August 2004.

This research project falls within the framework of the “Reference methodology” (MR-003). The sponsor signed a commitment of compliance with this “Reference methodology”.

This research has been registered on the site http://clinicaltrials.gov/.

X.2. CHANGES TO THE PROTOCOL

Any substantial change, i.e. any change that is likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of the research, on the quality and safety of the products tested, on the interpretation of scientific documents that support the conduct of the research or the way in which the research is conducted, is subject to a written amendment submitted to the sponsor. The latter must obtain, prior to its implementation, a favourable opinion from the CPP.

Non-substantial changes, i.e, those that do not have a significant impact on any aspect of the research, are communicated to the CPP for information.

All changes are validated by the sponsor, and by all research stakeholders involved in the change, before submission to the CPP. This validation may require the meeting of all committees formed for the research.

All changes to the protocol must be made known to all persons carrying out the research, who undertake to respect its contents.

XI. PRESERVATION OF RESEARCH DOCUMENTS AND DATA

The duration of the archiving period is defined by the sponsor according to the applicable procedures and regulations.
The patient data will be kept up to 2 years after the last publication of the research results, or, in absence of publication, until the final report of the research is written.
In accordance with the decree of 11th August 2008 fixing the period of storage by the sponsor and the investigator of documents and data relating to biomedical research other than that relating to medicinal products for human use, they will then be archived for a minimum period of 15 years.

Data processing operations of the investigator and other professionals involved in the conduct of the research may not be stored for more than 5 years after the end of the last research in which the person participated. They will be then archived for a minimum period of 15 years.

XII. RULES FOR PUBLICATION

XII.1. SCIENTIFIC COMMUNICATIONS

The analysis of data provided by the centre will be carried out by ATLANSTAT. The analysis will result in a written report, submitted to the sponsor. This report will allow for the preparation of one or more publication(s).

Any written or oral communication of the results of the research project must receive prior approval of the investigator and, if applicable, of any committee set up for the research project.

The publication of the main results will mention the name of the Sponsor, of all the people who included or followed-up research participants, of methodologists, biostatisticians and data managers who participated in the research, of members of the committee(s) set up for the research project. The international rules for writing and publishing shall be taken into account (IMCJE's *Uniform Requirements for Manuscripts*, April 2010).

The primary purpose of the sponsor is the use of these data for regulatory purposes.

XII.2. COMMUNICATION OF RESULTS TO PATIENTS

Upon their request, participants will be informed of the overall results of the research projects explained in the patient information.

XII.3. TRANSFER OF DATA

ATLANSTAT will ensure data management. The conditions for transferring all or part of the research database will be decided by the sponsor and be subject to a written agreement. The data will be transferred in a pseudonymized form, the study participant number will be used to identify the patient. Data transfer will be encrypted and no data transfer is planned outside the European Union.

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