Study OCI_2201

"A single center post-market clinical follow-up (PMCF) observational study evaluating the clinical performance and the safety profile of the JuniOrtho™ Telescopic Intramedullary Nail (JTIN) for the treatment of pediatric patients suffering from Osteogenesis Imperfecta"

Final Statistical Analysis Plan
Version 1.0, 09 January 2025

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Study code: OCI_2201

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STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Version 1.0, 09 January 2025

Study title: A single center post-market clinical follow-up (PMCF) observational study evaluating the clinical performance and the safety profile of the JuniOrtho™ Telescopic Intramedullary Nail (JTIN) for the treatment of pediatric patients suffering from Osteogenesis Imperfecta

Study code: OCI_2201

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1 GLOSSARY

Abbreviation	*Explanation*
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated serious adverse device effect
CE	Conformité Européenne (European Conformity)
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
FAS	Full Analysis Set
FAIS	The Full Analysis Implant Set
GCP	Good Clinical Practice
GP	General Practitioner
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
JTIN	JuniOrtho™ Telescopic Intramedullary Nail
Max	Maximum
MDDs	Medical Device Deficiencies
MDR	Medical Device Regulation (EU 2017/745)
Min	Minimum
OT	Operative Technique
OI	Osteogenesis Imperfecta
Q	Quarter
PMCF	Post-Market Clinical Follow-up
IFU	Instruction for Use
ITT	Intention-To-Treat
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
TMF	Trial Master File
ROM	Range of Motion
SOA	State-of-art
USADE	Unanticipated serious adverse device effect
WBP	Weight Bearing Protocol

2 INTRODUCTION

A manufacturer of a medical device must demonstrate that the intended purpose(s) and claim(s) made in relation to safety and performance of a medical device are achieved. As a general rule, such demonstration will require clinical data. Clinical data are relevant to the various aspects of the clinical safety and performance of the device. This may include data from prospective and retrospective clinical investigations of the concerned device as well as market experience of the same or equivalent devices and medical procedures and information from the scientific literature. The aim of the present study is to collect post-market clinical evidence (post-market clinical follow up PMCF) on the use of the medical device JuniOrtho™ Telescopic Intramedullary Nail (JTIN).

2.1 BACKGROUND INFORMATION

Osteogenesis Imperfecta (OI), also called brittle bone disease, is a group of genetic disorders that affect connective tissue due to a lack of type I collagen. The classical Sillence types of OI (types I-IV) with autosomal dominant inheritance comprise about 80-85% of cases and are caused by mutations in the genes that encode type I collagen, COL1A1 and COL1A2.
Osteogenesis imperfecta is a very polymorphic condition, apart from the classical autosomal dominant forms, there are also recessive forms, often severe. Forms with hyperthrophic calluses (type V DA), and others associated with joint contractures (Bruck's syndrome).
Currently, more than twenty affections are identified clinically and by molecular biology studies. The incidence of forms recognizable at birth is 1:10-20,000. The hallmark feature of OI is bone fragility, with susceptibility to fracture from minimal trauma, as well as bone deformity and growth deficiency. Secondary features include dentinogenesis imperfecta (DI), cardiopulmonary complications and, in adult years, hearing loss. The clinical features of OI represent a continuum ranging from perinatal lethality to individuals with severe skeletal deformities, mobility impairments, and very short stature to nearly asymptomatic individuals with a mild predisposition to fractures, normal dentition, normal stature, and normal life span.
Fractures can occur in any bone but are most common in the limbs.
Management is ideally done by a multidisciplinary team including specialists in medical management of OI, clinical genetics, orthopedics, endocrinologist, rehabilitation medicine, paediatric dentistry, otology/otolaryngology, and mental health.
Intramedullary nails have an important role for bone stabilization and fracture prevention in patients with OI, who suffer from bone fragility and recurrent fractures. Long bones in the lower limbs of OI patients are especially prone to deformities that develop as a result of bone deformability or from malunion in fractures. Thus, it is important to provide structural support to

the weakened bones of these patients, which is better accomplished with the use of intramedullary devices.

The objectives of long bone rodding in OI patients are to:

- Fracture treatment;
- Correct deformity;
- Improve function;
- Restore bone density through functional load bearing.

2.2 RATIONALE OF THE STUDY

Orthofix Srl put the JTIN on the European market (2021) by the mean of a pre-market clinical evaluation made under the Medical Device Directive (MDD) requirements that was based on the analysis of the scientific literature of equivalent devices.

This study has been planned as part of the Orthofix Srl post-market active surveillance plan for the collection of data on both the clinical performance and the safety profile of the JTIN in a representative population of patients and users.

The rationale of the proposed study is to update and support the pre-market clinical evaluation of the JTIN with real-word-evidence clinical data, in order to confirm the benefit/risk ratio of this medical device and to keep the CE mark under Medical Device Regulation (MDR) requirements.

The uniqueness of the pediatric population manifests itself in specific indications for lower extremity reconstruction, due to osteogenesis imperfecta; different approach in compliance with operative and postoperative care in addition to need for adaptability to rapid growth and development. The JuniOrtho™ Telescopic Intramedullary Nail (JTIN) is an established, marketed device, commercially available and used as standard device in orthopedic surgeries.

The post-marketing, prospective study with CE-marked device JuniOrtho™ Telescopic Intramedullary Nail (JTIN) is designed for gathering real-world medical data from treatment of fractures, osteotomies/ bone deformities, malunions and non-unions in femur and tibia in pediatric patients (older than 18 months) suffering from osteogenesis imperfecta.

All data will be gathered from standard medical documentation from patients who have already been successfully treated with JTIN. Additionally, all procedures that patients underwent are justified by standard of care.

Constant identification of serious or unexpected serious risk related to the use of the device, especially in real-world experience may bring additional data, that can contribute to the safety of future patients.

In conclusion, patients will not directly benefit from the participation in this study but no additional risk related to the study participation is to be recognized.

3 PROTOCOL AND CRF VERSION

Protocol version: MARTOM_OCI_2201_JTIN_V1.1_02082024 - signed

CRF version: JTIN_OCI_2201_Visits_eCRF vs.28.71_20Nov2024 and JTIN_OCI_2201_AE_MDD_eCRF vs 28.71_20Nov2024

4 OBJECTIVES OF THE ANALYSIS PLAN

The analysis plan proposed below describes the aspects needed to know about the study and the statistical analysis methods to be used to apply them to the data collected and respond to the study objectives.

5 PRIMARY STUDY OBJECTIVE

The primary objective of the study is to evaluate the clinical safety profile of JTIN within the scope of its intended purpose, when used according to the manufacturer IFU on a representative population of subjects and users.

6 SECONDARY STUDY OBJECTIVES

The secondary objective of the study is to evaluate the clinical safety and performance of JTIN by the three following endpoints, when the MD is used within the scope and according to the manufacturer IFU.

7 EXPLORATORY OBJECTIVE

The Gillette Functional Assessment Questionnaire will be collected, according to hospital standard care, before the surgery Visit 0 (screening)) and at 1 year follow up (Visit 6), to evaluate the changes after treatment.

The questionnaire is performed by the investigator the first time (i.e. before the surgery) observing the patient (in presence or eventually via telemedicine), and for the follow-up it can be performed by the investigator by telephone or by email with the parent (or legal representative).

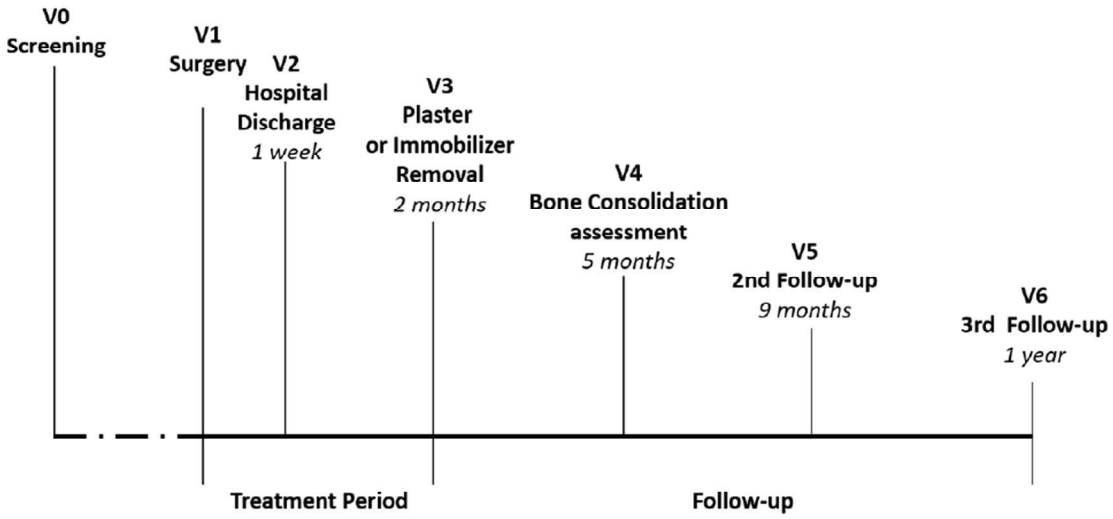
The Gillette Functional Assessment Questionnaire is not specific developed for OI patients but it is used in the hospital because no other score is currently available specifically for OI patients. The hospital is aware that other factors for OI patient can interfere with the score.

8 STUDY DESIGN

This is a Post Market Clinical Follow-up (PMCF) study which is prospective and retrospective, observational, single-center, not controlled.

No requirements regarding the treatment of patients will be imposed on the Site or Principal Investigator and the Sponsor will not in any manner influence the treatment decisions of Principal Investigator (i.e. non-interventional). The enrolment of patients and their treatment, including diagnostics and monitoring, will be guided solely by the principles of normal medical practice and the Principal Investigator's sole medical judgment. Site and Principal Investigator will ensure that the Device is used in accordance with normal medical practice and the instructions for use. The subjects will not undergo additional visit nor non-invasive, invasive or burdensome procedures additional to those performed under the normal clinical practice.

Figure1. Study schematic diagram



9 STUDY POPULATION

This study will be conducted only on patients with a regular indication for JTIN as per IFU (no off-label use will be included): the nail is indicated for fractures, osteotomies, malunions and non-unions in femur and tibia in pediatric patients suffering from osteogenesis imperfecta. The JTIN is intended to be used in pediatric patients, older than 18 months.

This study includes only one site (monocentric) located in Paris, France. The site was chosen for this study due to the number of subject devices already implanted, and the wideness of the indications covered by the surgeries. The site was also positively evaluated by sponsor for the appropriate qualification and competency of the investigator and of the staff, and availability of facilities and equipment.

Sample size calculation:

Due to the observational nature of the study, no formal sample size calculation has been done, but a revision of the literature on the complication rates (intended as at least one serious/not serious adverse event certainly or possibly related to the procedure up to 1 year follow-up) has been made. The scientific literature reports that the percentage of procedures which develop at least one serious/not serious adverse event certainly or possibly related to the procedure itself is between 9% and 60%, with a mean of 31%. Assuming a complication rate aligned or better than the mean observed in literature (31%), a sample size of 15 procedures will be sufficient to estimate the adverse event rate with the upper limit of the 95% confidence interval equal or lower than the worst complication rate seen in literature (i.e. 60%).

Starting from this sample size, to also assume that the success rate (intended as proportion of procedures that result in a bone union achieved) is aligned or better than the mean observed in literature (80%), 20 procedures will be needed.

Considering a drop-out or a non-evaluable rate of 20% of the procedures, a total of approximately 25 procedures should be made. Each subject could have from 1 to 4 procedures. Assuming the worst scenario of no more than 1 procedure for subjects, a maximum of 25 subjects needs to be enrolled. Anyway, the enrolment will stop when the total number of the procedures is reached.

10 STUDY DURATION

The study duration at the site is planned for 1,5 years (18 months), that includes the enrolment period of 6 months plus 1 year of data collection up to last patient last visit.

The study duration for each subject implant is approximately 1 year from the date of surgery, according to the visit schedule. Since the subjects will follow standard clinical care of the site and due to the observational character of the study, the study duration for each subject can be slightly different according to the standard of care.

11 INCLUSION CRITERIA

A patient will be included in the study if:

• is in pediatric age (> 18 month and < 18 years) at the time of surgery;

• is skeletally immature;

• has a diagnosis for OI;

• has a regular indication for surgical intervention with JTIN to treat femoral and/or tibial fractures, osteotomies, malunions and non-unions;

• Patient and/or legal representative is duly informed and doesn't oppose to participation.

12 EXCLUSION CRITERIA

A patient will not be included in the study who:

• has a medical condition that is a contraindication according to the manufacturer's instruction for use;

• has any conditions that in the Investigator's opinion may interfere with the study execution or due to which the patient should not participate for safety reasons;

• requires the application of, or has already in-situ the application of concomitant devices that cannot be safely removed (except for permitted concomitant devices paragraph);

• is participating in other clinical trials or has taken part in any clinical study in the last 3 months with exception of analytical trials on genetics study related to OI (i.e. studies that do not include an investigational treatment for the patient such as new drugs or other medical devices);

• is likely to be lost to follow up, according to investigator's opinion.

13 ANALYSIS POPULATION

- **The Full Analysis Set (FAS) population** will consist of all enrolled patients treated by the means of JTIN application and who didn't oppose to study participation. The FAS population will be used for all the analyses of the study that are presented at subject level.
- **The Full Analysis Implant Set (FAIS) population** will consist of all JTIN applications performed on subjects belonging to the FAS population. The FAIS population will be used for all the analyses of the study that are presented at implant level.

The CRF contains the selection criteria information in the form of a binary variable (Yes/No) for each element described. Patients are considered to belong to the FAS and FAIS populations if they indicate that they meet the selection criteria in the previously mentioned binary variables.

Several of these criteria can be verified with the data recorded in the CRF. The criteria to be verified to define the FAS and FAIS population for the analysis are described below:

INCLUSION CRITERIA

1. *is in pediatric age (> 18 month and < 18 years) at the time of surgery;* The patients' age at surgery must be between 18 months and 18 years.
2. *is skeletally immature;* This criteria cannot be verified with the variables included in the CRF.
3. *has a diagnosis for OI;* The variables "*OI Type Diagnosis"* and *"Treated bone"* should be collected in screening visit.
4. *has a regular indication for surgical intervention with JTIN to treat femoral and/or tibial fractures, osteotomies, malunions and non-unions;* The variable *"Intended use of JTIN for this case"* should be collected in screening visit.
5. *Patient and/or legal representative is duly informed and doesn't oppose to participation. T*his criteria cannot be verified with the variables included in the CRF.

EXCLUSION CRITERIA

1. *has a medical condition that is a contraindication according to the manufacturer's instruction for use;* This criteria cannot be verified with the variables included in the CRF.
2. *has any conditions that in the Investigator's opinion may interfere with the study execution or due to which the patient should not participate for safety reasons;* This criteria cannot be verified with the variables included in the CRF.
3. *requires the application of, or has already in-situ the application of concomitant devices that cannot be safely removed (except for permitted concomitant devices paragraph);* This criteria cannot be verified with the variables included in the CRF.

4. is participating in other clinical trials or has taken part in any clinical study in the last 3 months with exception of analytical trials on genetics study related to OI (i.e. studies that do not include an investigational treatment for the patient such as new drugs or other medical devices); This criteria cannot be verified with the variables included in the CRF.

5. is likely to be lost to follow up, according to investigator's opinion. This criteria cannot be verified with the variables included in the CRF.

A list of patients belonging to each of the populations will be sent to the sponsor for confirmation prior to analysis.

14 STATISTICAL ANALYSIS METHODS

The methods of analysis to be used for both objectives of the study and for description of the study variables are detailed below.

Quantitative variables will be described with measures of central tendency and dispersion: mean, median, SD (standard deviation), Q1 (first quartile) and Q3 (third quartile), minimum and maximum. Qualitative variables will be described using absolute and relative frequencies.

In the descriptive analysis of qualitative variables, two percentage columns will be presented, total percentage (%) and valid percentage (% valid), that are respectively, the percentage over the sum of valid responses plus missing values and the percentage over the total of valid responses.

Clopper-Pearson confidence intervals at 95.0% will be shown for the primary and secondary objectives.

For time-to-event variables (i.e. fracture free-survival) will be analysed using the Kaplan-Meier method. The median and the 95% CI as well as the number of events and patients censored will be provided. Error standard will be estimated per the method Greenwood (Greenwood, 1926). KM graphs will be presented along with the number of case-at-risk at exact time points.

Change in Gillette Functional Assessment Questionnaire from Screening to 1 year follow up will be analysed by means of descriptive statistics as a continuous variable. Comparisons will be performed by means of paired t-test (parametric) or Wilcoxon (non-parametric) depending on the distribution of the sample.

These tests will be used in all bilateral cases and with a level of significance of 0.05. In cases where a p-value less than 0.05 appears, it refers to the existence of statistical significance.

No imputation for missing data will be considered.

No adjustment for multiple comparisons will be performed.

Data will be analysed using SPSS v29.0 or later.

Interim Analysis: No interim analysis is planned.

15 DESCRIPTIVE STATISTICAL ANALYSIS

15.1 PATIENT DISPOSITION

A summary of patients included in the study, as well as those who are in each populations and the reasons for not belonging to one of the populations will be shown.

15.2 SCREENING AND ENROLMENT VISIT

15.3 DEMOGRAPHICS DATA BY PATIENT

This analysis will be performed on FAS population.

The categorical variables to be described are, N and (%):

- Number of procedures by patient
- Gender (Male / Female)

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- Age at surgery (calculated, in months, as date of surgery minus date of birth (year, month)) by patient at the first procedure
- Age at ICF signature (calculated, in months, as date of ICF signature minus date of birth (year, month)) by patient at the first procedure
- Height by patient at the first procedure
- Weight by patient at the first procedure
- BMI by patient at the first procedure

15.4 DEMOGRAPHICS DATA BY PROCEDURE

This analysis will be performed on FAIS population.

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- Age at surgery (calculated, in months, as date of surgery minus date of birth (year, month))
- Age at ICF signature (calculated, in months, as date of ICF signature minus date of birth (year, month))
- Height
- Weight
- BMI

The categorical variables to be described are, N and (%):

- Gender (Male / Female)

15.5 MEDICAL CONDICTIONS BY PATIENT

This analysis will be performed on FAS population.

The categorical variables to be described are, N and (%):

- Medical conditions by patient (Number of patients with **at least one**: (Yes / No)):
  - Autism spectrum disorder
  - Sickle cell disease (SCD)
  - Transient synovitis
  - Septic arthritis
  - Juvenile idiopathic arthritis
  - Cerebral palsy
  - Slipped Capital Femoral Epiphysis (SCFE)
  - Developmental Dysplasia of the Hip (DDH)
  - Blount's Disease
  - Neurogenic Hip Dysplasia
  - Ligamentary laxity
  - Legg–Calvé–Perthes disease
  - Spina bifida
  - Down Syndrome
  - Chromosomal aberration
  - Other (a list will be shown)
  - None
  - History of cardiovascular disease
  - History of diabetes

The categorical variables to be described are, N and (%):

- Family history of disease by patient (Number of patients with **at least one**: (Yes / No)):
  - Osteogenesis imperfecta
  - (Cardio)myopathy
  - Encephalopathy
  - Diabetes Mellitus
  - Hypertension/Cardiovascular disease
  - Thrombosis
  - Malignancy
  - Deafness
  - Renal disease
  - None of the above
  - Unknown

15.6 DIAGNOSIS & X-RAY IMAGES BY PROCEDURE

This analysis will be performed on FAIS population.

The categorical variables to be described are, N and (%):

- OI Type Diagnosis (Type I / Type II / Type III / Type IV / Type V / Type VI / Type VII / Type VIII)
- OI Type Diagnosis groups. A new variable will be calculated according to the following criteria*:
    - Mild/Non-deforming (Type I);
    - Severe (Type IV; Type V, Type VI);
    - Highly Severe/Progressively deforming (Type III, Type VII, Type VIII)
    - Lethal (Type II);

  *References: https://www.niams.nih.gov/health-topics/osteogenesis-imperfecta and https://pmc.ncbi.nlm.nih.gov/articles/PMC4314691/#tbl1.
- Treated bone (Femur / Tibia)
- Body side (Left / Right)
- Body side (Only Left / Only Right / Both). A new variable will be generated based on original variable body side. For procedures with only left, with only right and with both the variable "Treated bone (Femur / Tibia)" will be described separately.
- Intended use of JTIN for this case (Fracture treatment / Osteotomy fixation (e.g. for deformity correction, bone reinforcement) / Malunion treatment / Non-union treatment)
- Was in the bone another fixation device, before JTIN application? (Yes / No)
- Was a software used during pre-planning ? (Yes / No)
    - In case yes, Which software?
    - In case yes, What information you looked for on the software?
    - In case no, Is there a particular reason why a software was not used?
- Preoperative AP projection X-Ray
- Preoperative ML projection X-Ray
- Number of additional radiographic images to upload (1 / 2)

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- Time from date of fracture to Date of screening visit (calculated as Date of screening visit minus date of fracture)
- Time from date of fracture to surgery (calculated as date of surgery minus date of fracture)

15.7 PRE-OP CLINICAL EXAMINATION AND GILLETTE SCORE BY PROCEDURE

This analysis will be performed on FAIS population.

The categorical variables to be described are, N and (%):

- The patient can stand up? (Yes / No (Non-weight-bearing)), if 'Yes':
    - Pre operative Weight-bearing Protocol (if not prescribed by surgeon, report what is known) (Toe-touch weight-bearing (TTWB) / Partial weight-bearing (PWB)/ Full weight-bearing (FWB)
    - The patient walks? (Yes / No)
- How frequent did the patient reported pain at the affected limb before JTIN application? (Never / Some of the days / About half of the days / Most of the days /Everyday), is not equal to 'Never' VAS Pain Score according to the patient will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)
- Was the pain farmacologically treated? (Yes / No / unknown)
- Was the Gillet Score performed BEFORE the treatment with JTIN? (Yes / No) is equal to 'Yes' Gillette Functional Assessment Questionnaire result will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)

15.8 PRE-OP ROM

This analysis will be performed on FAIS population.

The categorical variables to be described are, N and (%):

- Which Range of Motion are available for this patient?
    - None
    - Knee Flexion
    - Knee Extension
    - Hip Flexion
    - Hip Extension
    - Hip Abduction
    - Hip Internal Rotation (supine)
    - Hip External Rotation (supine)
    - Ankle Joint Dorsiflexion
    - Ankle Joint Plantarflexion

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- ROM Knee Flexion

- ROM Knee Extension
- ROM Hip Flexion
- ROM Hip Extension
- ROM Hip Abduction
- ROM Hip Internal Rotation (supine)
- ROM Hip External Rotation (supine)
- ROM Ankle Joint Dorsiflexion
- ROM Ankle Joint Plantarflexion

16 SURGERY VISIT

This analysis will be performed on FAIS population.

16.1 DEVICE APPLICATION SURGERY

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Duration of the surgery (hours)

The categorical variables to be described are, N and (%):

- Was other fixation device removed from the same bone during this surgery? (Revision surgery) (Yes / No), if yes:
    - What device was removed? :
        - JTIN nail
        - Other telescopic nail
        - Non-telescopic rigid nail
        - Elastic nails
        - Plate
        - Screws
        - Other (a list will be shown)

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- Female rod diameter mm
- Diameter mm x 10
- Nail length mm
- Number length

The categorical variables to be described are, N and (%):

- Nail Product Code
    - 99-67735100
    - 99-67735120
    - 99-67735130
    - 99-67735140
    - 99-67735150
    - 99-67740130
    - 99-67740155
    - 99-67740180
    - 99-67740205
    - 99-67740230
    - 99-67745160
    - 99-67745175
    - 99-67745190
    - 99-67745205
    - 99-67745230
    - 99-67750250
    - 99-67750275
    - 99-67750300
    - 99-67750325
    - 99-67750350
    - 99-67760250
    - 99-67760275
    - 99-67760300
    - 99-67760325
    - 99-67760350
- If 'Nail Product Code' is equal to '99-67735100' answer this question:
    - Nail batch number (B1783051 / B2641703 / B3009814)
- If 'Nail Product Code' is equal to '99-67735120' answer this question:
    - Nail batch number (B1782950 / B2641683 / B2742622 / B4443378)
- If 'Nail Product Code' is equal to '99-67735130' answer this question:
    - Nail batch number (B1786577 / B1788041 / B2641704 / B2815658)
- If 'Nail Product Code' is equal to '99-67735140' answer this question:
    - Nail batch number (B1786575 / B1788107 / B2641702 / B3478907 / B3549910)
- If 'Nail Product Code' is equal to '99-67735150' answer this question:

    - Nail batch number (B1783016 / B1788040 / B2641701 / B2992850 / B4443379)
- If 'Nail Product Code' is equal to '99-67740130' answer this question:
    - Nail batch number (B1786576 / B1788109 / B1803399)
- If 'Nail Product Code' is equal to '99-67740155' answer this question:
    - Nail batch number (B1782964 / B1788110 / B1808958 / B2598629)
- If 'Nail Product Code' is equal to '99-67740180' answer this question:
    - Nail batch number (B1786609 / B1788104 / B1808957 / B2598628 / B2959917 / B3013876 / B3584086 / B3935695)
- If 'Nail Product Code' is equal to '99-67740205' answer this question:
    - Nail batch number (B1786622 / B1788105 / B2588616 / B3560929 / B4443313)
- If 'Nail Product Code' is equal to '99-67740230' answer this question:
    - Nail batch number (B1786621 / B1788039 / B1795858 / B3138829 / B3372939)
- If 'Nail Product Code' is equal to '99-67745160' answer this question:
    - Nail batch number (B1795495 / B2319444 / B2452597)
- If 'Nail Product Code' is equal to '99-67745175' answer this question:
    - Nail batch number (B1843786 / B2304454 / B2669626)
- If 'Nail Product Code' is equal to '99-67745190' answer this question:
    - Nail batch number (B1796858 / B2319443 / B2815657 / B3439975 / B4185631)
- If 'Nail Product Code' is equal to '99-67745205' answer this question:
    - Nail batch number (B1796857 / B3013875 / B4443312)
- If 'Nail Product Code' is equal to '99-67745230' answer this question:
    - Nail batch number (B1788625 / B1795239 / B1811305 / B3905681)
- If 'Nail Product Code' is equal to '99-67750250' answer this question:
    - Nail batch number (B1788627 / B2452596 / B2626613)
- if 'Nail Product Code' is equal to '99-67750275' answer this question:
    - Nail batch number (B1788629 / B1808956 / B2624778 / B3138828)
- If 'Nail Product Code' is equal to '99-67750300' answer this question:
    - Nail batch number (B1788628 / B1808850 / B3175772)
- If 'Nail Product Code' is equal to '99-67750325' answer this question:
    - Nail batch number (B1803398 / B3352050)
- If 'Nail Product Code' is equal to '99-67750350' answer this question:
    - Nail batch number (B1801940 / B2343541)
- If 'Nail Product Code' is equal to '99-67760250' answer this question:
    - Nail batch number (B2299500)
- If 'Nail Product Code' is equal to '99-67760275' answer this question:
    - Nail batch number (B2299495)

- If 'Nail Product Code' is equal to '99-67760300' answer this question:
  - Nail batch number (B1801939)
- If 'Nail Product Code' is equal to '99-67760325' answer this question:
  - Nail batch number (B1808849 / B3175768)
- If 'Nail Product Code' is equal to '99-67760350' answer this question:
  - Nail batch number (B1801938 / B3325975)
- Did the patient receive a blood transfusion? (Yes / No), if Yes:
  - How many BT unit were used, Mean, SD, Median, Q_1, Q_3, Min, Max will be described

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- How many x-ray images were taken?
- Radiant dose (Gy)

The categorical variables to be described are, N and (%):

- According to the investigator, was the objective of the surgery achieved? (Yes / No / Partially), if not or partially:
  - Please explain your answer and clarify what should be done to fulfil the treatment
  - Is another surgery recommended? (Yes / No), if yes:
    - Why is another surgery recommended?

Note.- Some patients may receive multiple implants during the same surgery. The use of multiple nails can affect surgery time and radiation dose. If multiple implants were used will be determined by identifying cases with the same patient ID and surgery date.

- The number of implants used in the same surgery will be shown (n,%)

In addition, the descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables based on the number of implants used in the same surgery:

- Radiant dose (Gy). The mean of the values reported for implants with the same date of surgery will be provided.
- Duration of the surgery (hours). The mean of the values reported for implants with the same date of surgery will be provided.

16.2 POST-OP RADIOGRAPHIC IMAGES

The categorical variables to be described are, N and (%):

- Post-op radiographic image: Medio-Lateral projection (ML)
- Post-op radiographic image: Antero-Posterior projection (AP)
- Number of additional radiographic images to upload (1 / 2)

17 DISCHARGE VISIT

This analysis will be performed on FAIS population.

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Time from surgery to Discharge (days) (calculated as Date of discharge minus date of surgery)

The categorical variable to be described is, N and (%):

- Time from surgery to Discharge (days) within the time windows estimated in the protocol (5-9 days)? (Yes / No)

18 PLASTER OR IMMOBILIZER REMOVAL VISIT

This analysis will be performed on FAIS population.

18.1 VISIT INFORMATION

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Time from surgery to date of removal (months) (calculated as Date of removal minus date of surgery)

The categorical variable to be described is, N and (%):

- Time from surgery to removal visit (months) within the time windows estimated in the protocol (1.5-2.5 months)? (Yes / No)

18.2 CLINICAL EXAMINATION

The categorical variables to be described are, N and (%):

- Has the bone reached a satisfactory consolidation? (Yes / No / Partially)
- The patient can stand up? (Yes / No (Non-weight-bearing)), if 'Yes':
    - Weight-bearing Protocol (if not prescribed by surgeon, report what is known) (Toe-touch weight-bearing (TTWB) / Partial weight-bearing (PWB)/ Full weight-bearing (FWB)
    - The patient walks? (Yes / No)
- How frequent did the patient reported pain at the affected limb before JTIN application? (Never / Some of the days / About half of the days / Most of the days /Everyday), is not equal to 'Never' VAS Pain Score according to the patient will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)
- Was the pain farmacologically treated? (Yes / No / unknown)

18.3 RADIOGRAPHIC IMAGES

The categorical variables to be described are, N and (%):

- Radiographic image: Medio-Lateral projection (ML)
- Radiographic image: Antero-Posterior projection (AP)
- Number of additional radiographic images to upload (1 / 2)

19 BONE CONSOLIDATION VISIT

This analysis will be performed on FAIS population.

19.1 VISIT INFORMATION

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Time from surgery to Bone Consolidation visit (months) (calculated as Date of bone consolidation minus date of surgery)

The categorical variable to be described is, N and (%):

- Time from surgery to Bone Consolidation visit (months) within the time windows estimated in the protocol (3-7 months)? (Yes / No)

19.2 CLINICAL EXAMINATION

The categorical variables to be described are, N and (%):

- Has the bone reached a satisfactory consolidation? (Yes / No / Partially), is not equal to 'Yes' answer this question:
    - Bone consolidation is expected at this visit, please explain why the patient didn't reach bone consolidation
- The patient can stand up? (Yes / No (Non-weight-bearing)), if 'Yes':
    - Weight-bearing Protocol (if not prescribed by surgeon, report what is known) (Toe-touch weight-bearing (TTWB) / Partial weight-bearing (PWB)/ Full weight-bearing (FWB)
    - The patient walks? (Yes / No)
- Calculation double, If 'Calculation double' is equal to '1' answer this question
    - Explain why the patient cannot stand if bone is consolidated
- How frequent did the patient reported pain at the affected limb before JTIN application? (Never / Some of the days / About half of the days / Most of the days /Everyday), is not equal to 'Never' VAS Pain Score according to the patient will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)
- Was the pain farmacologically treated? (Yes / No / unknown)

19.3 ROM (RANGE OF MOTION)

The categorical variables to be described are, N and (%):

- Which Range of Motion are available for this patient?
    - None

- Knee Flexion
- Knee Extension
- Hip Flexion
- Hip Extension
- Hip Abduction
- Hip Internal Rotation (supine)
- Hip External Rotation (supine)
- Ankle Joint Dorsiflexion
- Ankle Joint Plantarflexion

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- ROM Knee Flexion
- ROM Knee Extension
- ROM Hip Flexion
- ROM Hip Extension
- ROM Hip Abduction
- ROM Hip Internal Rotation (supine)
- ROM Hip External Rotation (supine)
- ROM Ankle Joint Dorsiflexion
- ROM Ankle Joint Plantarflexion

19.4 RADIOGRAPHIC IMAGES

The categorical variables to be described are, N and (%):

- Radiographic image: Medio-Lateral projection (ML)
- Radiographic image: Antero-Posterior projection (AP)
- Number of additional radiographic images to upload (1 / 2)

20 2ND FOLLOW-UP VISIT

This analysis will be performed on FAIS population.

20.1 VISIT INFORMATION

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Time from surgery to 2nd follow up visit (months) (calculated as 2nd follow visit Date minus date of surgery)

The categorical variable to be described is, N and (%):

- Time from surgery to 2nd follow up visit (months) within the time windows estimated in the protocol (8-10 months)? (Yes / No)

20.2 CLINICAL EXAMINATION

The categorical variables to be described are, N and (%):

- Has the bone maintained a satisfactory consolidation? (Yes / No / Partially), is not equal to 'Yes' answer this question:
    - Bone consolidation is expected at this visit, please explain why the patient didn't reach bone consolidation and if there is any change between previous visit:
- The patient can stand up? (Yes / No (Non-weight-bearing)), if 'Yes':
    - Weight-bearing Protocol (if not prescribed by surgeon, report what is known) (Toe-touch weight-bearing (TTWB) / Partial weight-bearing (PWB)/ Full weight-bearing (FWB)
    - The patient walks? (Yes / No)
- Calculation double, If 'Calculation double' is equal to '1' answer this question
    - Explain why the patient cannot stand if bone is consolidated
- How frequent did the patient reported pain at the affected limb before JTIN application? (Never / Some of the days / About half of the days / Most of the days /Everyday), is not equal to 'Never' VAS Pain Score according to the patient will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)
- Was the pain farmacologically treated? (Yes / No / unknown)

20.3 ROM (RANGE OF MOTION)

The categorical variables to be described are, N and (%):

- Which Range of Motion are available for this patient?
    - None
    - Knee Flexion
    - Knee Extension
    - Hip Flexion
    - Hip Extension
    - Hip Abduction
    - Hip Internal Rotation (supine)
    - Hip External Rotation (supine)
    - Ankle Joint Dorsiflexion
    - Ankle Joint Plantarflexion

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- ROM Knee Flexion
- ROM Knee Extension
- ROM Hip Flexion
- ROM Hip Extension
- ROM Hip Abduction
- ROM Hip Internal Rotation (supine)
- ROM Hip External Rotation (supine)
- ROM Ankle Joint Dorsiflexion
- ROM Ankle Joint Plantarflexion

21 3ER FOLLOW-UP VISIT

This analysis will be performed on FAIS population.

21.1 VISIT INFORMATION

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Time from surgery to 3er follow up visit (months) (calculated as 3er follow visit Date minus date of surgery)

The categorical variable to be described is, N and (%):

- Time from surgery to 3er follow up visit (months) within the time windows estimated in the protocol (23-25 months)? (Yes / No)

21.2 CLINICAL EXAMINATION

The categorical variables to be described are, N and (%):

- Has the bone maintained a satisfactory consolidation? (Yes / No / Partially), is not equal to 'Yes' answer this question:
  - Bone consolidation is expected at this visit, please explain why the patient didn't reach bone consolidation and if there is any change between previous visit:
- The patient can stand up? (Yes / No (Non-weight-bearing)), if 'Yes':
  - Weight-bearing Protocol (if not prescribed by surgeon, report what is known) (Toe-touch weight-bearing (TTWB) / Partial weight-bearing (PWB)/ Full weight-bearing (FWB)
  - The patient walks? (Yes / No)
- Calculation double, If 'Calculation double' is equal to '1' answer this question
  - Explain why the patient cannot stand if bone is consolidated

- How frequent did the patient reported pain at the affected limb before JTIN application? (Never / Some of the days / About half of the days / Most of the days /Everyday), is not equal to 'Never' VAS Pain Score according to the patient will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)
- Was the pain farmacologically treated? (Yes / No / unknown)
- Was the Gillet Score performed at this visit? (Yes / No) is equal to 'Yes' Gillette Functional Assessment Questionnaire result will be described (Mean, SD, Median, Q_1, Q_3, Min, Max)

21.3 ROM (RANGE OF MOTION)

The categorical variables to be described are, N and (%):

- Which Range of Motion are available for this patient?
    - None
    - Knee Flexion
    - Knee Extension
    - Hip Flexion
    - Hip Extension
    - Hip Abduction
    - Hip Internal Rotation (supine)
    - Hip External Rotation (supine)
    - Ankle Joint Dorsiflexion
    - Ankle Joint Plantarflexion

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variables:

- ROM Knee Flexion
- ROM Knee Extension
- ROM Hip Flexion
- ROM Hip Extension
- ROM Hip Abduction
- ROM Hip Internal Rotation (supine)
- ROM Hip External Rotation (supine)
- ROM Ankle Joint Dorsiflexion
- ROM Ankle Joint Plantarflexion

21.4 RADIOGRAPHIC IMAGES

The categorical variables to be described are, N and (%):

- Radiographic image: Medio-Lateral projection (ML)

- Radiographic image: Antero-Posterior projection (AP)
- Number of additional radiographic images to upload (1 / 2)

22 STUDY EXIT VISIT

This analysis will be performed on FAIS population.

The categorical variables to be described are, N and (%):

- Reason for study exit
    - Subject completed protocol last visit
    - Nail removed
    - Subject does not meet inclusion criteria (a list will be shown)
    - Subject withdrew consent
    - Subject withdrawn by Investigator (a list will be shown)
    - Subject Death
    - Lost to follow-up
    - Subject had an AE that does not permit the continuation of the study (specify nr. of AE: a list will be shown)
    - Other Reason (a list will be shown)

23 PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the clinical safety profile of JTIN within the scope of its intended purpose, when used according to the manufacturer IFU on a representative population of subjects and users.
To fulfil this objective, one safety endpoint will be evaluated:
• Percentage (%) of procedures with at least one serious/not serious adverse event certainly or possibly related to JTIN up to 1 year follow-up.

This objective will be analysed through the descriptive analysis of the variables as detailed bellow:
This analysis will be performed on FAS/FAIS population.

23.1 ADVERSE EVENTS

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Patients with at least one adverse event
- Patients with at least one serious adverse event
- Patients with at least one related adverse event (considering related as Yes, certainly related and Yes, possibly)
- Patients with at least one serious related adverse event (considering related as Yes, certainly related and Yes, possibly)
- Procedures with at least one adverse event
- Procedures with at least one serious adverse event
- Procedures with at least one related adverse event (considering related as Yes, certainly related and Yes, possibly)
- Procedures with at least one serious related adverse event considering related as Yes, certainly related and Yes, possibly)

23.1.1 ADVERSE EVENTS DESCRIPTION

The categorical variables to be described are, N and (%):

- Adverse Event Description by patient (at least once)

- If "***'Unanticipated/Other adverse event (specify below)***" is selected, the following question: "Adverse Event System Organ Class," will be shown by patient (at least one)

- Adverse Event Description by procedure (at least once)
  - If "***'Unanticipated/Other adverse event (specify below)***" is selected, the following question: "Adverse Event System Organ Class," will be shown by procedure (at least one)

23.1.2 RELATED ADVERSE EVENTS

For each Adverse Event description collected, the categorical variable to be described is, N and (%):

- According to the investigator, is this AE related to the Investigational Medical Device (JTIN) and relative procedures? Yes, certainly related / Yes, possibly related / Not related

23.1.3 ADVERSE EVENTS SERIOUS

For each Adverse Event description collected, the categorical variable to be described is, N and (%):

- Seriousness Adverse Event: Serious / Not serious

For each Serious Adverse Event description collected, the categorical variables to be described are, N and (%):

- The Adverse Event is considered serious because the patient:
  - Death
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or a body function including chronic diseases
  - In-patient or prolonged hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or impairment
  - Fetal distress, fetal death or, a congenital abnormality, or birth defect

23.1.4 ADVERSE EVENTS LIST

A list with adverse events collected and its characteristics will be shown.

23.2 MEDICAL DEVICE DEFICIENCIES (MDD)

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Patients with at least one MDD
- Procedures with at least one MDD

23.2.1 MEDICAL DEVICE DEFICIENCIES (MDD) TYPES AND DESCRIPTION

The categorical variables to be described are, N and (%):

- Type of Device Deficiency by patient (at least once)
- Type of Device Deficiency by procedure (at least once)
- For each type of Deficiency collected Its "corresponding MDD description" will be shown

For each type of Deficiency collected, the categorical variables to be described are, N and (%):

- Did this MDD resulted in an Adverse Event for the patient? (Yes / No)
- Could surgery be completed with the device in question? (Yes / No / Not applicable)
- Was an additional surgery required following device failure? (Yes / No)

23.2.2 MEDICAL DEVICE DEFICIENCIES (MDD) LIST

A list with MDD collected and its characteristics will be shown.

24 SECONDARY OBJECTIVE

The secondary objective of the study is to evaluate the clinical safety and performance of JTIN by the three following endpoints, when the MD is used within the scope and according to the manufacturer IFU:

• Implant survival rate: percentage of not exchanged nails up to 1 year follow-up (safety);

• Bone union achievement (performance);

• Post-treatment fracture-free survival up to 1 year follow-up (performance)

This analysis will be performed on FAS/FAIS population.

24.1 IMPLANT SURVIVAL RATE

Implant survival rate: percentage of not exchanged nails up to 1 year follow-up.

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Number of procedures that Reason for study exit= Nail removed vs other reason

24.2 BONE UNION ACHIEVEMENT

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Number of procedures that reached a satisfactory bone consolidation in any visit (considering at the first visit in which the answer is “Yes” in “Has the bone reached a satisfactory consolidation?” variables in removal or bone consolidation visits)
- Number of patients that reached a satisfactory bone consolidation in any visit or procedure (considering at the first visit in which the answer is “Yes” in “Has the bone reached a satisfactory consolidation?” variables in removal or bone consolidation visits)

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Time to full a satisfactory bone consolidation from surgery (months), per procedure, considering at the first visit in which the answer is “Yes” in “Has the bone reached a

satisfactory consolidation?" variables in removal or bone consolidation visits. Calculated as date of first consolidation minus date of surgery.

A list with bone consolidation variables will be shown.

24.3 POST TREATMENT FRACTURE-FREE SURVIVAL

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Number of patients with fracture(s) occurred (variable: "Bone fracture during or after treatment" in adverse event description + confirmation that the bone with fracture is the same where there is the implant*) in at least one procedure
- Number of procedures with fracture(s) occurred (variable: "Bone fracture during or after treatment" in adverse event description + confirmation that the bone with fracture is the same where there is the implant*)

* A list, with confirmation for each AE that the "fracture" is on the same bone or not, will be provide from Sponsor in order to confirm if the bone with fracture is the same where there is the implant.

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Time to free fracture from surgery (months), per procedure, considered at the first Adverse Event onset date in which variable: "Bone fracture during or after treatment" in adverse event description has been checked. Calculated as the first adverse event onset date with a "Bone fracture during or after treatment" minus date of surgery.

Kaplan-Meier analyses will be provided for Time to free fracture. The median and the 95%CI as well as the number of events and patients censored will be provided.

The number of patients at risk will be displayed.

Event: if "Bone fracture during or after treatment" in adverse event description is clicked (which first occurs).

Time: Time to free fracture from surgery, as has been defined above.

24.4 WEIGHT BEARING GRADE

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Number of procedures that reached a Full weight-bearing (FWB) from surgery in any visit
- Number of Patients that reached a Full weight-bearing (FWB) from surgery in any visit or procedure

The descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Time to Full weight-bearing from surgery (months), per procedure, considered at the first date in which the answer is "'Full weight-bearing (FWB)" in "Weight bearing protocol assigned" variables. Calculated as date of the first visit of Full weight-bearing minus date of surgery.

A list with Weight bearing grade variables will be shown.

25 EXPLORATORY OBJECTIVE

Gillette Functional Assessment Questionnaire will be collected before the surgery and then at bone consolidation assessment and at 1 year follow-up.

This analysis will be performed on FAIS population.

The descriptive statistic (Mean, SD, Median, Q1, Q3, Min, Max) will be shown for the following continuous variable in the screening and 3er follow up visits per procedure, for the overall population and for subgroups of patients defined according to OI Type Diagnosis (Mild/Non-deforming / Severe / Highly Severe/Progressively deforming / Lethal) as defined in section 15.6 of this document:

- Gillette Functional Assessment Questionnaire result

Comparisons will be performed using paired t-test (parametric) or Wilcoxon (non-parametric) depending on the distribution of the sample.

26 CONCOMITANT MEDICATION

The type of drug group by patient will be described (N, %) considering the patient has taken at least once.

27 REFERENCES

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