Study OCI_2206

"Observational retrospective study to assess the clinical benefit and safety profile of the intramedullary nail CHIMAERA in adult patient who have suffered pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur in daily practice: CHIMAERA Study"

Statistical Analysis Plan Final
Version 1.0, 06 March 2024

Sponsor:
Orthofix S.r.l.,
Via Delle Nazioni 9
37012 Bussolengo (Verona), Italy
Contact Person: Edo Knijff
email: edoknijff@orthofix.it
Office landline: (+39) 045 6719 000

Study code: OCI_2206

Prepared by: Laura Casas (Biostatistician Lead-Evidenze Clinical Research)

Approved by: Orthofix S.r.l.

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

Version 1.0, 6 March 2024

Study title: Observational retrospective study to assess the clinical benefit and safety profile of the intramedullary nail CHIMAERA in adult patient who have suffered pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur in daily practice: CHIMAERA Study

Study code: OCI_2206

	SIGNATURE	DATE
SPONSOR: Daniela Cangiano (Clinical Program Manager) **Arianna Dettori (Clinical Research Associate)**	Daniela Cangiano Daniela Cangiano (Mar 6, 2024 14:11 GMT+1) Arianna Dettori Arianna Dettori (Mar 6, 2024 14:12 GMT+1)	Mar 6, 2024 Mar 6, 2024
CRO: Laura Casas (Biostatistician Lead-Evidenze Clinical Research)	CASAS HERRERO LAURA - 03464891X Firmado digitalmente por CASAS HERRERO LAURA - 03464891X Fecha: 2024.03.06 12:18:17 +01'00'	

TABLE OF CONTENTS

1 GLOSSARY

Abbreviation	*Explanation*
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated serious adverse device effect
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
DB	Database
DHS	Dynamic Hip Screw
DPD	Data Protection Delegate
FAS	Full Analysis Set
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IC	Informed Consent
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFU	Instructions for Use
Max	Maximun
MDD	Medical Device Deficiency
MDR	Medical Device Regulation
Min	Minumun
MR	Magnetic Resonance
PMCF	Post Market Clinical Follow-up
Q	Quarter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
THA	Total Hip Arthroplasty
TMF	Trial Master File
USADE	Unanticipated serious adverse device effect

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

Bone fractures are most common in youth and in the elderly, with differences in incidence over time and between regions. Of all the fractures recorded in older population, it is important to note that these occur mainly in the hip, affecting approximately 6% of the male population and 18% of females. With the rapid increase in the elderly population, the annual worldwide incidence of hip fractures is estimated to be up to 21.3 million by 2050. Hip fractures have an incidence of approximately 1 per 1000 head of population in western countries and are associated with a very

significant cost to any healthcare system. The number of patients hospitalized due to hip fracture has been reported to be around 620,000 in the European Union.

Hip fracture is the general term for fracture of the proximal (upper) femur. These fractures can be subdivided into trochanteric, subtrochanteric, pertrochanteric and intertrochanteric fractures. These terms reflect the proximity of these fractures to the greater and lesser trochanters, which are two bony protuberances (bulges) at the upper end of the femur outside the joint capsule.

The most common site was the intertrochanteric region which approximately accounted for 50%. There is a 15% mortality rate among elderly patients with intertrochanteric fractures, which accounts for the highest mortality rate for all hip fractures among this age group. Subtrochanteric fractures involve the segment of the proximal femur from the lesser trochanter to the isthmus. The major fracture involves a zone between the inferior border of the lesser trochanter and the junction of the proximal and middle one third of the femur (approximately a 5-cm segment). The subtrochanteric femoral fractures, which account for 10–34% of all hip fractures. Although subtrochanteric fractures are the least frequent type of hip fracture, they provide unique challenges because of the inherent instability of the fracture fragments. These fractures are notorious for intraoperative difficulty in reduction and post-operative complications like non-union and malunion. Anatomically, surgical reduction is difficult in subtrochanteric fractures because of the muscles attached to fractured fragments generates various deforming forces.

Underlying causes of hip fractures are most commonly low-energy trauma (e.g., falling), high-energy trauma (e.g., traffic accidents) or pathological lesions (e.g., osteoporosis, cancer). Fractures caused by hig-h-energy injuries happen in both genders and in all ages. However, spontaneous fractures or fractures resulting from mild injuries are only found in older individuals. Pathologic lesions affecting the skeletal system in adults are most often caused by metastatic disease, being the most common site outside of the axial skeleton, the femur. Another common cause of hip fracture events, particularly in older population, is osteoporosis. Osteoporosis is a group of bone disorders of diminished bone resorption due to osteoclastic abnormality resulting in hard and brittle bones. When pathologic femur fractures occur, they are associated with increases in morbidity and mortality.

Hip fractures are a leading cause of disability and mortality among adult population, with 1-year mortality surpassing 20%. Survivors often experience diminished walking ability, reduced activities of daily living, and loss of independence. Despite the development in implant technology and surgical techniques, the mortality rates remained similar: 24% in the 1980s to 23% in the 1990s, and to 21% after 1999 ($p = 0.7$). In addition to the direct economic impact of hip fracture treatment, there is a considerable societal impact because elderly hip fracture patients are at risk for increased rate of mortality, inability to return to prior living circumstances, the need for an increased level of care and supervision, decreased quality of life, decreased level

of mobility and ambulation, and secondary osteoporotic fractures, including a second or contralateral side hip fracture.

Therefore, due to the high incidence of hip fractures in adult population and the great economic and psychosocial burden it entails, it is important to treat them adequately. Currently, there are different treatment options, differentiating between non-operative treatment and operative treatment.

Non-operative treatments are mainly focused on those patients who may be non-ambulatory, with valgus-impacted femoral neck fractures, or medically unfit for general anesthesia. Most trochanteric fractures are usually non-operative since some parts of the trochanter and not all of it are involved, the abductor mechanism is usually not affected, reason why treatment is mainly symptomatic. In subtrochanteric fractures is usually performed with traction by distal femur pin traction and formation of 90-90 traction (hip and knee in 90° flexion) that is performed only on children and patients with medical comorbidities who do not tolerate surgery or general anesthesia. Finally, for intertrochanteric fractures, a conservative treatment by immobilization carries the risk of high morbidity and mortality, so early surgical intervention is indicated for early mobilization and to increase survival rate.

To gain the safe mobility in early time, operative intervention, which can provide strength and stability of the fracture fixation, is the primary goal of treatment. Among the operative treatments, we can highlight the plating systems, external fixation, Total Hip Arthroplasty (THA) and hemiarthoplasty, dynamic hip screw (DHS) and intramedullary nailing.

The plating systems minimizes operative trauma by way of two small percutaneous portals, and small-diameter drilling prevents additional bone damage in the remaining lateral trochanteric wall. This device is indicated for the treatment of pertrochanteric and basicervical fractures with intact lateral walls, consisting of a plate of a predetermined length with three diaphyseal screws and two telescopic cervical screws angled at 135◦ to the plate to allow controlled fracture compression. The theoretical advantages of this design are the provision of rotational stability, by using two screws in the femoral neck, and a reduction in the lateral cortical damage, which can be created by a 12-mm single drill hole.

External fixation was initially introduced for intertrochanteric fractures at about the same time as DHS was used, however, since the early results of external fixations were not so encouraging, the method was overshadowed by the use of DHS which had become the standard treatment in the last few decades. Specific advantages of plate fixation include that the technique is simple, direct visual control of the fracture fragment and biomechanically more rigid fixation and stability which requires minimal postoperative immobilization. Disadvantages include the direct approach to the fracture site increases the risk of infection, the scar is longer and subsequent lengthening maybe more common. Refracture may occur, as stress shielding results in thinning of the cortices. Removal of the material is associated with specific morbidity.

THA is an effective treatment for unstable intertrochanteric fracture with the loss of posteromedial cortex support, a fracture pattern that is unlikely to be reduced satisfactorily using a intramedullary nail, with serious osteoporosis; with ipsilateral femoral head necrosis or osteoarthritis. In patients who are physiologically fit and have failed conservative management, THA can provide appropriate pain control and functional restoration. If the patient is an independent individual and cooperative and has a normal pattern of daily living, THA will be performed, and if the patient is old with conscious disorder and is not cooperative and lives at home most of the time, hemiarthroplasty would be a suitable treatment. Complications after conversion THA after previous fracture fixation are, predictably, higher than in cases of primary THA. In the perioperative period, patients have longer surgeries, with greater blood loss and longer hospital stays. In the postoperative period, instability, heterotopic ossification, infection, leg length discrepancy, nerve injury, and loosening have been the major reported complications. DHS is an extramedullary fixation system, which consist in an implant which has a nail, or screw, which is passed up the femoral neck to the femoral head, used most commonly in intertrochanteric fractures. These are considered 'dynamic' implants as they have the capacity for sliding at the plate/screw junction to allow for collapse at the fracture site. For this conventional procedure, the lateral vastus muscle must be split broadly (10 cm), which is associated with significant soft tissue damage and inevitable blood loss, both of which may worsen multiple existing comorbidities of elderly patients.

Intramedullary nailing of proximal femur fractures is characteristically performed via a cephalocondylic approach, with the insertion of a metal nail through the greater trochanter, but is also used for reverse oblique and unstable fractures. The biomechanical rationale of using the intramedullary nailing in unstable trochanteric fractures is that the weight-bearing force acts through a shorter lever arm from the center of hip rotation, thereby placing less stress on the implant. Internal fixation is the treatment of choice for the subtrochanteric femoral fractures aiming to obtain the best stability for early mobilization and reduces the complications associated with prolonged recumbency with the maximum restoration of function. Proximal femoral nail (PFN) and Gamma nail are two most commonly used devices in the intramedullary fixation. PFN has become prevalent in treatment of intertrochanteric fractures in recent years because it was improved by addition of an antirotation hip screw proximal to the main lag screw. However, both benefits and technical failures of PFN have been reported. There is a debate on whether the short or long nails have been more beneficial for patients with hip fractures. Short nails are more cost-effective and are associated with less operating room time and blood loss and ensuring a good biomechanical stability; however, lack adequate diaphyseal fixation leading to increased pain or fracture risk at the tip of the implant. On the other hand, long nails may decrease periimplant fracture rate by spanning entire femoral diaphysis.

Intramedullary nailing systems used for hip fracture are generally associated with improved functional outcomes compared to the baseline and comparable complication rates with the other treatment options. Several meta-analyses and systematic reviews demonstrated that, the intramedullary nailing is a safe and effective option for different hip fracture patterns with similar safety profile. In terms of clinical benefit, results shown a bone union range of 93%-98% with an average of 98.3% while in terms of safety profile, results shown a range rate of reoperations due to ADEs/SADEs range of 0.0%-27.5% with an average of 5.9%.

2.2 RATIONALE OF THE CLINICAL INVESTIGATION

CHIMAERA™ is an internal fixation system designed for Intramedullary nailing fixation intended for insertion into the medullary canal of a femur in individuals suffering from stable and unstable pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur.
This study has been planned as part of the Orthofix S.r.l post-market active surveillance plan for data collection on both the clinical performance and the safety profile of the CHIMAERA™.
The MDR (EU) 2017/745 states that demonstration of compliance with the general performance and safety should be based on clinical data that, for class II devices and implantable devices should, as a general rule, be sourced from clinical investigations that have been carried out under the responsibility of a sponsor.
The rationale of the proposed study is to update and support the pre-market clinical evaluation of the CHIMAERA™ with Real World Evidence clinical data in a real-life surgical setting, in order to confirm the benefit/risk ratio of this medical device in terms of clinical benefit and safety profile and to keep the CE mark under MDR requirements.

3 PROTOCOL AND CRF VERSION

Protocol version: Version 1.0_13.07.2023

CRF version: eCRF_ENG_V0_13/07/2023

4 OBJECTIVE AND DESIGN

5 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.

6 PRIMARY STUDY OBJECTIVE

The primary objective of this study is to evaluate the clinical benefit of the long variant of the CHIMAERA™ used in adult patients according to the manufacturer IFU in routine clinical practice from the time of surgery within 12 months follow-up after nail implant.

7 SECONDARY STUDY OBJECTIVES

The secondary objective of this study is to evaluate the safety profile of the long variant of the CHIMAERA™ used in adult patients according to the manufacturer IFU in routine clinical practice since nail application until 6 months after nail implant.

8 STUDY DESIGN

The CHIMAERA study is designed as a retrospective, non-interventional, multicenter, PMCF study intended to evaluate both clinical benefit and safety profile of CHIMAERA™ device in adult patients according to the manufacturer IFU in routine clinical practice.

The study has been designed to retrospectively analyze the patient's medical records of patients who underwent a surgical implantation of CHIMAERA™ part of the site routine clinical practice. Data collection will be carried out during the study observation period, from the surgery until the last follow-up visit within 12-months after nail implant. Information will be collected from the different evaluations made by the subject in accordance with routine clinical practice, including the day of surgery, the hospital discharge, the bone consolidation assessment (1st follow up visit), the second follow up visit (2nd follow up visit), the last follow-up visit (3rd follow up visit), and additional surgeries if it occurred within 12 months after nail implant. Surgeons belonging to the 2 study sites who will participate in the study must have full awareness of orthopedic fixation procedures and should be familiar with the devices, instruments and surgical procedure, including the application and removal. After reviewing the selection criteria and confirming patient eligibility, demographic, and clinical and safety information from the time of surgery until the last follow-up visit will be collected from medical records.

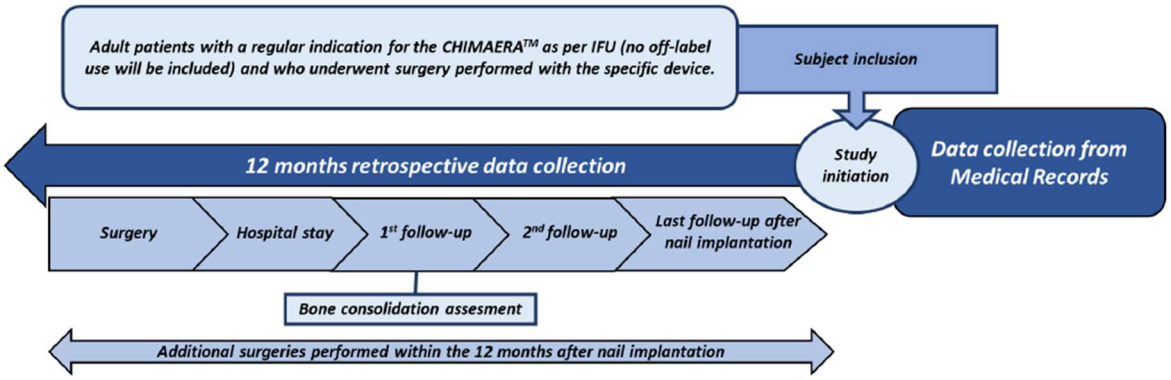
To ensure the observational nature of the study, study data (demographics, clinical performance and safety data) will be collected from data already recorded in the medical records according to routine clinical practice. No diagnostic or therapeutic intervention outside of routine clinical practice will be applied.

The use of primary data sources is justified since it can provide the information needed to answer the primary objective in a cost-effective manner and using already available data. Patients' medical records are expected to contain all the required information. Due to the pure retrospective design of the study with exclusive use of primary data sources, no study visit will be required, but according to local legislation, it will be essential that before collecting any information from medical records, participants or their guardians are asked for informed consent (IC). Once the IC is signed and the patient's eligibility is confirmed, the investigator will initiate accurate and appropriate data collection.

Due to the retrospective nature of the study, the decision on the prescription of Intramedullary nailing technique with CHIMAERA™ was under the discretion of the physician and it was made prior to the inclusion of the patient in the study. All participant patients had already undergone surgery through the intramedullary nailing technique using CHIMAERA™ under clinical practice conditions.

Individual patient data will be collected as pseudonymized in an electronic database designed specifically for this study.

Figure1. Study schematic diagram



9 STUDY POPULATION

It is planned to include non-competitively a consecutively a maximum of 44 subjects, from 2 sites in Italy, meeting the inclusion and exclusion criteria (Considering an imprecision of 5%) in two investigational sites located both in Italy. Clinical data will be collected only on adult patients with a regular indication for the CHIMAERA™ as per IFU (no off-label use will be included) and who underwent surgery performed with the specific device.

Sample size calculation:

The sample size calculation is based on the number of patients that allow the consecution of the study primary objective: *to evaluate the clinical benefit of the long variant of the CHIMAERA™ used in adult patients according to the IFU in routine clinical practice from the time of surgery within 12 months follow-up after nail implant.* The clinical benefit will be evaluated with the percentage of patients in which achieved bone union within 12 months from the nail implant.

The scientific literature reports that the percentage of patients in which bone union rate was achieved is 98.3% (IC95% 93%-100%). Assuming a bone union rate aligned or better than the weighted mean observed in literature (98.3%) with a confidence interval between 93% and 100% using a bilateral confidence interval with an alpha error of 5%, a sample size among 120 and 44 patients would be needed to estimate this proportion with an imprecision of 5%.

Table 1. Sample size considering different Expected Proportions

Confidence Level	Expected proportion	Sample Size (N)
95%	93%	120
95%	94%	107
95%	95%	94
95%	96%	81
95%	97%	98
95%	98.3%	51
95%	99.9%	44

For this clinical study, the sample size of 44 patients was chosen. The choice is based on sales data and considering the available timeframe of implanted nails. The study is designed to analyze medical records of adult patients who underwent CHIMAERA™ implantation from 2018 to 2023 in the standard clinical practice setting.

10 STUDY DURATION

The study will start in 4Q 2023, but these times may be modified by the administrative processing periods for initiation of the study. The enrolment period will be for 3 months, and the study will last approximately 6 months from the start of recruitment until the report of results.

11 INCLUSION CRITERIA

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Patients who had a regular indication for surgical intervention with the long variant of CHIMAERA™ according to the manufacturer's IFU.
2. Patients equal or older than 18 years at the time of surgery.
3. Patients who underwent surgery performed with CHIMAERA™.
4. Patients with clinical data registered in her/his medical records sufficient to assess the safety and efficacy endpoints of the study.

12 EXCLUSION CRITERIA

Patients eligible for inclusion in this study must not meet any of the following criteria:

1. The patient expressed his willingness to participate in the Study by signing and dating informed consent.
2. Patient who had/has a medical condition that is a contraindication according to the manufacturer's instruction for use leaflet.
3. Patient has been diagnosed with bilateral proximal femur fractures.
4. Patient who needed the application of, or had already in-situ a concomitant not permitted device which cannot be safely removed.
5. Patient with other concurrent medical or non-medical conditions that in the opinion of the participating investigator may prevent participation or otherwise render the patient ineligible for the study.
6. The patient is participating in other clinical studies, or he/she has participated in other clinical studies in the 3 months prior signing the informed consent.

13 ANALYSIS POPULATION

- **The full analysis set (FAS) population** consists of all patients included in the study after selection criteria review, patients who meet all selection criteria. The CRF contains the screening criteria information in the form of a binary variable (Yes/No) for each item described. The full analysis set will be used for all descriptive analysis.
- **The clinical benefit population** consists of patients who have available data that allow the primary efficacy endpoint assessment. The clinical benefit population will be used for primary objective (see primary objective section).
- **The safety population** includes all adult patients in whom CHIMAERA™ has been used. It includes all patients who have undergone an intramedullary nailing technique with the CHIMAERA™ medical device. The safety analysis will be performed in the “safety population” which includes all patients who have undergone an intramedullary nailing technique with the CHIMAERA™ medical device.

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 will be shown at 95.0%.

No imputation for missing data will be considered.

Data will be analysed using SPSS v29.0 or later

Interim Analysis: During the study development and if the sponsor considers it necessary, an interim analysis could be performed after at least 22 subjects will be enrolled and completed the treatment in which bone union has been achieved within 12 months from the nail implant in order to preliminary confirm the results obtained.

No adjustment for multiple comparisons will be performed.

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.

16 SCREENING VISIT

16.1 DEMOGRAPHIC DATA

This analysis will be performed on FAS 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 as date of surgery minus date of birth)
- Age at ICF signature (calculated as date of ICF signature minus date of birth)
- Height
- Weight
- BMI

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

- Gender (Male / Female)
- Race (Caucasian, African, Asian , Other (a list will be shown))

16.2 ANAMNESIS

This analysis will be performed on FAS population.

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

- Did the patient work at the time of surgery? YES / NO
- Was the patient a smoker? YES / NO, If “YES”, descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) of the number of cigarettes per day will be shown
- Did the patient drink alcoholic beverages? YES / NO, If “YES”, the frequency will be shown:
    - Occasionally
    - During meals
    - Several times a day even outside meals
- Comorbidities:

- Osteoporosis
- Diabetes
- Tumor
- Other (a list will be shown)
- Does the patient take medication regularly? YES / NO, If "YES", type and dosage will be shown.

16.3 CLINICAL DIAGNOSIS

This analysis will be performed on FAS population.

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

- Time from date of trauma (calculated as date of ICF signature minus date of trauma)

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

- Clinical diagnosis (Non pathological fracture / Non-union)
- Classification of Fracture (31A / 31B / 31C)
    - If select 31A, Choose one of these subgroups will be described: 31A 1.1 / 31A 1.2 / 31A 1.3 /31A 2.2 / 31A 2.3 / 31A 3.1 / 31A 3.2 / 31A 3.3
    - Was there a second fracture in the femoral shaft extending distally to a point approximately 10cm proximal to the intercondylar notch? YES / NO, If “YES” Choose one of these subgroups will be described: 32A, 32B, 32C:
        - If selected 32A, Choose one of these subgroups will be described: 32A1 / 32A2 32A3
        - If selected 32B, Choose one of these subgroups will be described 32B2 / 32B3
        - If selected 32C, Choose one of these subgroups will be described: 32C2 / 32C3
    - Which is the cause of the fracture? (Trauma / Other)
        - If trauma will be described: High energy Low energy Info not available / Other (a list will be shown)
    - Are RX (AP + ML) related to diagnosis available? YES / NO

17 SURGERY VISIT

This analysis will be performed on FAS population.

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

- Treated Femur (Left / Right)
- Distal diameter of the nail (10 mm / 11mm)
- CCD angle (125° / 130°)
- Length of the nail (280 mm / 300 mm / 320 mm / 340 mm / 360 mm / 380 mm / 400 mm / 420 mm / 440 mm / 460 mm)
- The main proximal lag screw is sliding or fixed? (Sliding / Fixed)
- Was the additional (optional) proximal screw also applied? YES / NO
- Was the nail distally locked? YES / NO, If “YES”, a static or dynamic locking or a secondary dynamization? will be described (Static / Dynamic / Secondary Dynamization)
- In addition to the nail, were additional synthetic media applied? YES / NO, If “YES”, the additional method used will be described

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

- Duration of the surgery skin to skin (hours)

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

- Has the patient been transfused? YES / NO, If “YES”, descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) of the number of used blood bags will be shown
- Are intraoperative fluoroscopies (AP + ML) or, preferably, RX (AP + ML) available in the short post-operative period related to the final nail placement? YES / NO

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

- Xap (mm)
- Dap (mm)
- Xlat (mm)
- Dlat (mm)
- TAD (mm)

18 DISCHARGE VISIT

This analysis will be performed on FAS 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 (1-20 days)? (Yes / No)

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

- Was any medication prescribed to the patient due to the surgery? YES / NO, If “YES” will be described:
    - Antibiotic
    - Anti-inflammatory
    - Analgesic
    - Heparin
    - Other (A list will be shown)
- Did the patient refer any info related to pain at the site of nail application? YES / Data not available), If “YES” will be described:
    - No pain
    - Pain

19 FIRST FOLLOW UP VISIT (1 MONTH)

This analysis will be performed on FAS 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 first follow up visit (months) (calculated as Date of first follow up minus date of surgery)

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

- Time from surgery to first follow up visit (months) within the time windows estimated in the protocol (1-3 months)? (Yes / No)

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

- Was the patient examined on an outpatient basis or contacted by telephone because he was unable to reach your hospital? (Outpatient visit / Telephone contact)
- Have the medications the patient takes regularly changed? YES / NO, If "YES", type and dosage will be shown.
- Did the patient refer any info related to pain at the site of nail application? YES / Data not available), If “YES” will be described:
    - No pain
    - Pain
- Are follow up fluoroscopies (AP + ML) or, preferably, RX (AP + ML) available? YES / NO

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

- Xap (mm)
- Dap (mm)
- Xlat (mm)
- Dlat (mm)
- TAD (mm)

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

- Observer 1: According to medical opinion, is/are the fracture/s treated with Chimaera nail consolidated? YES / NO, If "NO", motivate will be described
- Observer 2: According to medical opinion, is/are the fracture/s treated with Chimaera nail consolidated? YES / NO, If "NO", motivate will be described.

- Number of patients in which consolidation has been achieved according to the two observers.

20 SECOND FOLLOW UP VISIT (6 MONTHS)

This analysis will be performed on FAS 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 second follow up visit (months) (calculated as Date of second follow up minus date of surgery)

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

- Time from surgery to second follow up visit (months) within the time windows estimated in the protocol (3-9 months)? (Yes / No)

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

- Was the patient examined on an outpatient basis or contacted by telephone because he was unable to reach your hospital? (Outpatient visit / Telephone contact)
- Have the medications the patient takes regularly changed? YES / NO, If "YES", type and dosage will be shown.
- Did the patient refer any info related to pain at the site of nail application? YES / Data not available), If “YES” will be described:
    - No pain
    - Pain

21 THIRD FOLLOW UP VISIT (12 MONTHS)

This analysis will be performed on FAS 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 third follow up visit (days) (calculated as Date of third follow up minus date of surgery)

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

- Time from surgery to third follow up visit (months) within the time windows estimated in the protocol (9-15 months)? (Yes / No)

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

- Was the patient examined on an outpatient basis or contacted by telephone because he was unable to reach your hospital? (Outpatient visit / Telephone contact)
- Have the medications the patient takes regularly changed? YES / NO, If "YES", type and dosage will be shown.
- Did the patient refer any info related to pain at the site of nail application? YES / Data not available), If “YES” will be described:
    - No pain
    - Pain
- During the year did the patient come back to work? (YES / NO / At time of surgery the patient didn’t work at all / Data not available)
- Are follow up fluoroscopies (AP + ML) or, preferably, RX (AP + ML) available? YES / NO

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

- Xap (mm)
- Dap (mm)
- Xlat (mm)
- Dlat (mm)
- TAD (mm)

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

- Observer 1: According to medical opinion, is/are the fracture/s treated with Chimaera nail consolidated? YES / NO, If "NO", motivate will be described
- Observer 2: According to medical opinion, is/are the fracture/s treated with Chimaera nail consolidated? YES / NO, If "NO", motivate will be described.

- Number of patients in which consolidation has been achieved according to the two observers.

22 DISCONTINUATION VISIT

This analysis will be performed on FAS population.

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

- Reason the patient was discontinued

23 PRIMARY OBJECTIVE

Primary objective: the primary objective of this study is to evaluate the clinical benefit of the long variant of the CHIMAERA™ used in adult patients according to the IFU in routine clinical practice from the time of surgery within 12 months follow-up after nail implant.

This analysis will be performed on the clinical benefit population.

The clinical benefit analysis will be performed in those patients who meet the following criteria:
- Patient has achieved bone union at the 12 months follow-up visit and this is the only evaluation available.
- Patient has achieved bone union at first follow-up this being the only evaluation available.
- Patient has both bone union evaluations completed (first follow up visit and last follow up visit) and achieved bony union at the end of the follow-up period. (considered a responder)
- Patient underwent reoperation but the reason for this was secondary dynamization. *If it will be indicated 'secondary dynamization' in ADDITIONAL SURGERY the patient will be included in this analyses (all other no).*
- Patient with fractures on the upper limbs not caused by the CHIMAERATM (e.g. simply stumbled or had a car accident) . *ADVERSE EVENTS section, answer "Unanticipated/Other adverse event (specify below)" specifying that an upper limb fractures occurred, but is "not related" to Chimaera (question "According to medical opinion, is the Adverse Event related to Chimaera?") (if it is collected any upper limbs fractures "related" to Chimaera in the question "unanticipated/Other adverse event", the patient will not be included in the analyses (not belong to clinical benefit population).*
- Patient underwent reoperation after first bone union evaluation. FU visit 1 or 3: the observer 1 and observer 2 certify that the bone union has been assessed. *Those patients in which the answers where "YES" and subsequently underwent a reoperation in ADDITIONAL SURGERY will be included (excluded the option "secondary dynamization").*
- Patient who has not suffered contralateral leg fracture. *EXCLUSION CRITERIA " Has the patient been diagnosed with bilateral proximal femur fractures? YES / NO" should be "NO".*
- Patient in whom no refraction occurred where the nail was applied. *This is to be found in ADVERSE EVENT (if it is marked 'bone fracture' the patient will not be included in this analyses).*

The categorical variable to be described is, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well:

- Number of patients that reached consolidation according to the two observer`s opinion in at least one visit (visit 1 or visit 3). Only if both evaluations are positive in each visit, the treatment goal will be considered achieved.

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

- Time to consolidation from surgery (months), considered at the first visit in which the answer is “Yes” in “According to medical opinion, is/are the fracture/s treated with Chimaera nail consolidated?” variables in both observers. Calculated as date of first date of consolidation minus date of surgery.

A list with consolidation variables will be shown.

24 SECONDARY OBJECTIVES

Secondary objective: to evaluate the safety profile of the long variant of the CHIMAERA™ used in adult patients according to the manufacturer IFU in routine clinical practice from the time of surgery until 6 months follow-up after nail implant.

The safety analysis will be performed in the safety population.

24.1 ADDITIONAL SURGERY

24.1.1 ADDITIONAL SURGERY DESCRIPTION

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well:

- Patients with at least one additional surgery
- Number of additional surgeries per patient
- What is the reason of additional surgery? (Adverse Event / Device Deficiency / Secondary dynamization / Other (a list will be shown))
- Number of patients with at least one additional surgery which reason was Adverse Event
- Number of patients with at least one additional surgery which reason was Device Deficiency
- Number of patients with at least one additional surgery which reason was Adverse Secondary dynamization
- Number of patients with at least one additional surgery which occurs in surgery visit
- Number of patients with at least one additional surgery which occurs in discharge visit
- Number of patients with at least one additional surgery which occurs in follow up visit 1
- Number of patients with at least one additional surgery which occurs in follow up visit 2
- Number of patients with at least one additional surgery which occurs in follow up visit 3

For the total number of additional surgeries, the descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) will be shown for the following continuous variable:

- Duration of the surgery (skin to skin) (minutes)

For the total number of additional surgeries, the categorical variables to be described are, N and (%):

- Has the patient been transfused? YES / NO, If “YES”, descriptive statistic (Mean, SD, Median, Q_1, Q_3, Min, Max) of the number of used blood bags will be shown

24.1.1 ADDITIONAL SURGERY LIST

A list with additional surgeries collected and its characteristics will be shown.

24.2 ADVERSE EVENTS

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well:

- 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 Possible, Probable and Casual relationship)
- Patients with at least one adverse event which require additional surgery

24.2.1 ADVERSE EVENTS DESCRIPTION

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

- Adverse Event Description by patient
    - If “Unanticipated/Other adverse event” is selected, the following question: “To which macro group do the adverse event belong?”, will be shown by patient.

24.2.2 RELATED ADVERSE EVENTS

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

- Adverse Event Description for each: Not related / Possible / Probable / Casual relationship

24.2.1 ADDITIONAL SURGERY ADVERSE EVENTS

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

- Did the adverse event require an additional surgery? YES / NO

- If NO, Could the device deficiency have led to an additional surgery? YES / NO
- Adverse Event Description for each: Require additional surgery / No require additional surgery

24.2.2 ADVERSE EVENTS SERIOUSNESS

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

- Adverse Event Description: Seriousness / Not seriousness

24.2.3 ADVERSE EVENTS LIST

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

24.3 DEVICE DEFICIENCIES (DD)

The categorical variables to be described are, N and (%) and Clopper-Pearson confidence intervals will be shown at 95.0% as well:

- Patients with at least one DD

24.3.1 DEVICE DEFICIENCIES (DD) TYPES AND DESCRIPTION

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

- Deficiency description by patient

24.3.2 DEVICE DEFICIENCIES (DD) RESULTED IN AN ADVERSE EVENT FOR THE PATIENT

For each DD, the categorical variables to be described are, N and (%):

- Did this DD resulted in an Adverse Event for the patient? by patient YES / NO, If the answer is YES
  - Are any other patient's clinical evaluation related to the event (i.e. labs results, autopsy etc.) available? YES / NO
  - Is it an expected Device Deficiency (listed in the IFU of the product)? YES / NO, if NO the macro group will be described.

24.3.3 DEVICE DEFICIENCIES (DD) REQUIRE AN ADDITIONAL SURGERY

For each DD , the categorical variables to be described are, N and (%):

- Did the device deficiency require an additional surgery? YES / NO
  - IF YES, Could surgery be completed with the device in question? YES / NO / Not applicable

        - Was a replacement device immediately available to complete surgery? YES / NO
        - did the event lead to a clinically relevant increase in the duration of the surgical procedure? YES / NO
        - Is a copy of the operative reports available for the medical evaluation? YES / NO (
    - IF NO, Could the device deficiency have led to an additional surgery? YES / NO / Not applicable
- Are x-ray of the deficiency device available? YES / NO / Not applicable
- Are any other patient's clinical evaluation related to the event (i.e labs results, autopsy etc.) available? YES / NO

24.3.4 DEVICE DEFICIENCIES (DD) LIST

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