1. CLINICAL INVESTIGATION PLAN IDENTIFICATION

Clinical Investigation Plan (CIP)

Post-Market Clinical Follow-up Observational Study

13/07/2023

V1.0

CI code: **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

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4. LIST OF ABBREVIATIONS

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
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
MDD	Medical Device Deficiency
MDR	Medical Device Regulation
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

5. SYNOPSIS

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
ACRONYM	CHIMAERA
INVESTIGATIONAL DEVICE	Orthofix® Chimaera Hip Fracture System™
PROCEDURES	The CHIMERA study intends to evaluate the clinical benefits of the study medical/investigational device in the standard clinical practice. The study will be conducted in two sites located in Italy; both considered reference sites for the treatment of adult patients with pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur, where the usage of Orthofix® Chimaera Hip Fracture System™ (from now on CHIMAERA™) was part of the normal clinical practice. The CHIMAERA™, is an internal fixation system intended 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 alone or when these fractures occur in combination with shaft fractures extending distally to a point approximately 10cm proximal to the intercondylar notch. The participant investigators will retrospectively include a maximum of 44 patients meeting inclusion and exclusion criteria (considering an imprecision of 5%) that will contribute for approximately 44 patients in which CHIMAERA™ was used. 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. No diagnostic or therapeutic intervention outside routine clinical practice will be applied. At inclusion, data will be retrospectively collected from patient medical records since the surgery and up to 12 months follow-up after nail implant. No study visit will be performed. Medical records of the participating sites 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 specific informed consent to be signed by them before any collection of patient information takes place.
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 manufacturer Instructions For Use (IFU) in routine clinical

	practice from the time of surgery within 12 months follow-up after nail implant.
SECONDARY OBJECTIVE	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 from the time of surgery until 6 months follow-up after nail implant.
TYPE OF THE INVESTIGATION	This clinical investigation is a post-market, retrospective, observational, multicenter study, namely a Post Market Clinical Follow-up (PMCF) study. By definition, it is designed as a single arm and will not involve randomization.
PLANNED INVESTIGATION PERIOD	**Planned data collection** *3 months* **Start of data collection** *3Q 2023* **End of data collection** *3Q 2024*
STUDY DURATION PER SUBJECT	Not applicable
CENTER(S) / COUNTRY(IES)	**Hospital** / **Country (EU)** / **City** / **Principal Investigator** 2 / Italy / Florence and Caserta / Prof. Roberto Civinini and Dr Gaetano Bruno
PATIENTS	It is planned to include 44 patients from 2 sites in Italy. Clinical data will be collected only from patients with a regular indication for CHIMAERA™ as per IFU (no off-label use will be included) and who underwent surgery performed with the specific device.
INCLUSION CRITERIA	Patients eligible for inclusion in this study must meet all of the following criteria: 1. The patient expressed his willingness to participate in the Study by signing and dating informed consent. 2. Patients who had a regular indication for surgical intervention with the long variant of CHIMAERA™ according to the manufacturer's IFU. 3. Patients equal or older than 18 years at the time of surgery. 4. Patients who underwent surgery performed with CHIMAERA™. 5. Patients with clinical data registered in her/his medical records sufficient to assess the safety and efficacy endpoints of the study.
EXCLUSION CRITERIA	Patients eligible for inclusion in this study must not meet any of the following criteria: 1. Patient who had/has a medical condition that is a contraindication according to the manufacturer's IFU leaflet. 2. Patient has been diagnosed with bilateral proximal femur fractures. 3. Patient who needed the application of, or ha already in-situ a concomitant not permitted device which cannot be safely removed.

	4. Patient with other concurrent medical or non-medical condition that in the opinion of the participating investigator may prevent participation or otherwise render the patient ineligible for the study. *5.* 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
CONCOMITANT MEDICATION/CON-COMITANT DEVICE	K-wires, bone graft and any other concomitant devices, i.e. bone screws, that were applied to fix any bone fragments but that were not considered critical for the maintenance of treated bone alignment, are permitted during the study. Examples of not permitted devices on the same CHIMAERA™-treated bone: plates providing fixation; external fixators; other intramedullary nails or elastic nails. It is understood that any necessary medical devices applied on any other bones than the one treated by CHIMAERA™ are permitted.
PRIMARY EFFICACY ENDPOINTS	The clinical benefit of CHIMAERA™ will be assessed by the percentage of patients in which bone union has been achieved within 12 months from the nail implant. 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 (first follow up visit and last follow up visit) completed and achieved bone union at the end of the follow-up period. (considered a responder) - Patient underwent reoperation but the reason for this was secondary dynamization. - Patient with fractures on the upper limbs not caused by the CHIMAERA™ (e.g. simply stumbled or had a car accident) - Patient underwent reoperation after first bone union evaluation. - Patient who has not suffered contralateral leg fracture. - Patient in whom no refraction occurred where the nail was applied. A double evaluation will be required (observer 1 and observer 2). Only if both evaluations are positive, the treatment goal will be considered achieved.
SECONDARY TOLERABILITY / SAFETY ENDPOINTS	The safety profile of CHIMAERA™ will be assessed through the percentage of patients that required a reoperation (i.e., additional surgery) caused by at least one of the following safety events:

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- Expected or unexpected adverse effect potentially or certainly related to the CHIMAERA™ (Adverse Device Effects (ADEs)/Serious Adverse Device Effects (SADEs)) since the nail application until until 6 months follow-up after nail implant.
- Medical Device Deficiency (MDDs) (i.e., breaking, loosening, or bending of the nail or of the screws) that caused an effect on the patient since the nail application until 6 months follow-up after nail implant.

All the reoperations that have occurred are considered but also those that have not occurred but that could have occurred (e.g., a patient who had a cut out but for any reasons has not been operated). It should be considered also all ADE/SADE/MDD that could have caused an additional operation.
</td></tr>
<tr><td>STATISTICAL METHODOLOGY</td><td>

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%) (1-26). 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 CHIMAERATM implantation from 2018 to 2023 in the standard clinical practice setting.

Statistical methodology:
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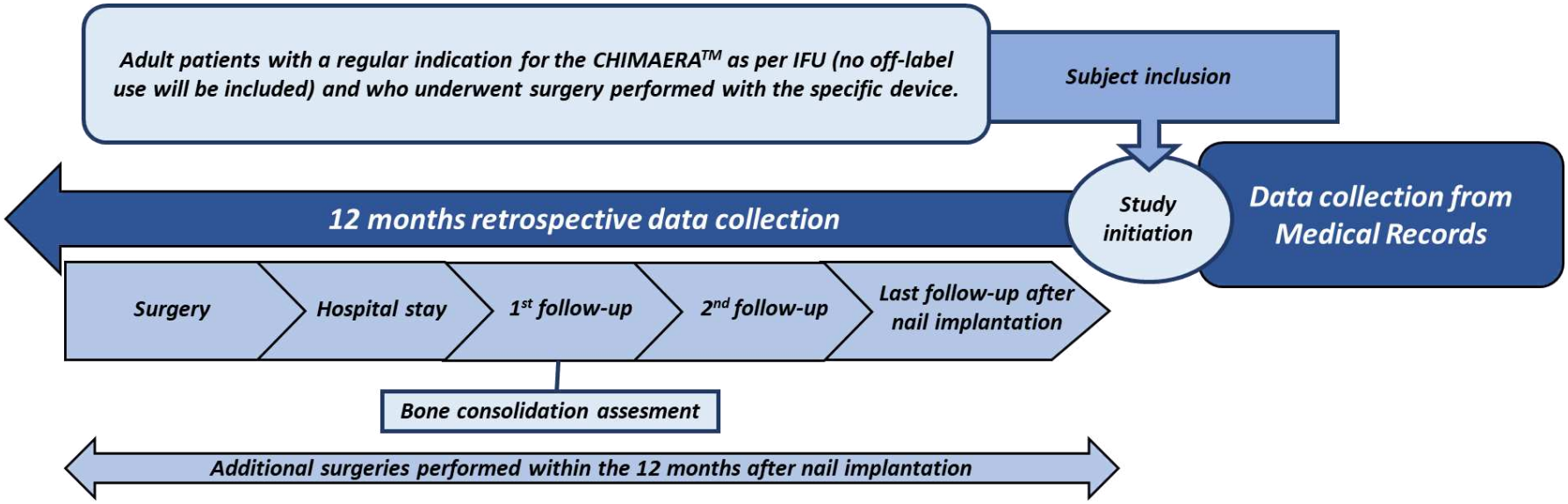
	Analysis will be performed using IBM SPSS Vs 22.0. When an inferential analysis is required, parametric tests will be used for continuous variables and nonparametric tests in the case of ordinal or categorical or nonparametric variables. All hypothesis tests will be two-sided and with a significance level of 0.05. For variables not fitting a normal (or parametric) distribution, the Mann-Whitney test (for unpaired data) and the Wilcoxon test (paired data) will be used. Contingency tables and the comparison of proportions and/or frequency distributions will be analyzed using the chi-square test (or Fischer's exact test when appropriate) will be used. 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. It is required a double evaluation with two positive opinions from both observers (observer 1 and observer 2) to consider the treatment goal achieved. The number and percentage of patients in which bone union was achieved will be provided both as continuous and categorical variables. The 95% CI will also be presented. 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" which includes all patients who have undergone an intramedullary nailing technique with the CHIMAERA™ medical device. The number and percentage of patients that required a reoperation due to at least one ADE/SADE/MDD will be calculated with a 95% confidence interval (CI). An analysis will be carried out according to degree of severity, seriousness and relationship with the medical device. All the reoperations that have occurred are considered but also those that have not occurred but that could have occurred (e.g., a patient who had a cut out but for any reasons has not been operated). It should be considered also all ADE/SADE/MDD that could have caused an additional operation. Therefore, the number and percentage of patients that hypothetically would have caused a reoperation due to at least one safety event will be described and calculated with a 95% CI.

5.1 Schematic Diagram

Figure 5:1 Study schematic diagram



6. INTRODUCTION

This document is a Clinical Investigation Plan for a human research study to be conducted according to the ethical principles set out in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Tripartite Harmonised Guidelines for Good Clinical Practice and the legislation and normative on Clinical Trials and Medical Devices (ISO14155: 2020 regulating Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice) (27), data protection (Regulation (EU) 2016/679 of the European Parliament and the Council, on 26 April 2016, GDPR first implemented on 25 May 2018), national and international regulations in force (the Medical Devices Regulation (MDR) (EU) 2017/745 of 5 April 2017) and its guidelines as MDCG 2020-10/1 and any further local applicable regulations (28, 29).

6.1 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.(30) 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.(31-40) 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.(37) The number of patients hospitalized due to hip fracture has been reported to be around 620,000 in the European Union.(41)

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. (34, 42)

The most common site was the intertrochanteric region which approximately accounted for 50%. (33, 43-48) 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.(49, 50) 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).(51-53) The subtrochanteric femoral fractures, which account for 10–34% of all hip fractures. (51, 52, 54) Although subtrochanteric fractures are the least frequent type of hip fracture, they provide unique challenges because of the inherent instability of the fracture fragments. (40, 55) These fractures are notorious for intraoperative difficulty in reduction and post-operative complications like non-union and malunion.(47) Anatomically, surgical reduction is difficult in subtrochanteric fractures because of the muscles attached to fractured fragments generates various deforming forces.(56)

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 high-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. (57) 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 (58). 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.(59, 60) When pathologic femur fractures occur, they are associated with increases in morbidity and mortality. (58)

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. (30, 61, 62) 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 ($p = 0.7$).(63) 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. (64, 65)

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.(38) 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. (57) 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. (57) 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.(66)

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. (43) 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. (67) 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. (44, 68)

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.(69) 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 (70, 71). 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. (72)

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.(73) In patients who are physiologically fit and have failed conservative management, THA can provide appropriate pain control and functional restoration. (74) 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. (57) 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. (74)

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. (34, 75) 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.(34) 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. (44, 68)

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. (76, 77) 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. (78) 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. (54) 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. (79-81) 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.(82-84) On the other hand, long nails may decrease periimplant fracture rate by spanning entire femoral diaphysis.(82, 83)

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%. (1-26)

6.2 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 (28)

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.

7. STUDY OBJECTIVES

7.1 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 manufacturer IFU in routine clinical practice from the time of surgery within 12 months follow-up after nail implant.

7.2 Secondary 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

8.1 Research Type

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.

Data collection will be carried during 4Q 2023-1Q 2024.

8.2 Subjects and Sites Numbers

It is planned to include non-competitively a consecutively a maximum of 44 subjects 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.

8.3 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 enrollment period will be for 3 months, and the study will last approximately 6 months from the start of recruitment until the report of results.

Start of data collection (Start of recruitment)	4Q 2023
End of data collection	1Q 2024
Database lock	1Q 2024
Statistical analysis	2Q 2024
Final report on operations and results	2Q 2024
Study duration	12 months

8.4 Measures to Minimize or Avoid Bias

The herein proposed study design presents some methodological limitations that deserve to be highlighted. First, this study was designed to collect available information derived from clinical practice, so some of the assessments might not be available for some participants or at certain evaluations. Therefore, a reporting bias could occur. This bias refers to errors introduced during the measurement of study variables, which may affect the study results and estimates. To minimize this risk of bias, unavailable data/assessments will be declared as unavailable and left as missing in the statistical analysis. However, it is expected that most of the data of interest in this study will be recorded in the medical records, as they are part of the usual clinical practice of these patients in Italy.

In addition, the possible occurrence of selection bias cannot be ruled out. However, to minimize their occurrence, the investigator will begin inclusion of patients in the study with the last patient meeting the inclusion/exclusion criteria. It will then continue with the inclusion of patients meeting the inclusion/exclusion criteria following a chronological order prospectively over time according to the list of subjects with a regular indication for CHIMAERA™ as per IFU.

On the other hand, the fact that it is a multicenter study that includes information in different ways could generate variability in data collection between study sites and countries. This variability is part of real clinical practice and is therefore an intrinsic limitation of this type of study.

Finally, like most observational studies, potential confounding bias should be considered. When an exposure of interest is strongly associated with another exposure that is also related to the outcome, confounding bias could exist. According to previous data obtained with the use of CHIMAERA™, in the present study it is expected that the results obtained from the primary endpoint regarding the clinical benefit will be in line with those obtained in previous studies in order to support the pre-market clinical evaluation of the CHIMAERA™ with Real World Evidence clinical data in a real-life surgical setting confirming his benefit/risk ratio.

8.5 Prematurely End of the Study (EOS)

The end of study is defined as all close out visits and database lock performed.

This study may be prematurely terminated by decision of the regulatory authorities or at the sponsor's discretion. This decision will be communicated in writing to the investigator.

The study sponsor has the right to replace a site at any time for poor recruitment, poor Clinical Investigation Plan adherence, inaccurate or incomplete data recording, noncompliance with the Guidelines for Good Pharmacoepidemiology Practice or any other pertinent local law or guideline.

Likewise, if the investigator decides to withdraw from the study, he/she must notify the sponsor immediately in writing.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Subject 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.

9.2 Subject 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.

10. TREATMENT OF SUBJECTS

10.1 Study Investigational Product(s)

The CHIMAERA™, is an internal fixation system 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. Its unique and distinguishing feature is the revolutionary locking mechanism of the lag screw that efficiently secures it to the nail without the need for a set screw. This implant is composed by 2 nails of sterile titanium (1 short and 1 long) with diameters of 10 and 11 mm for distal and 15.5 mm for proximal, differents lenghts comprises from 280 to 450 mm and with a 125° or 130° CCD angle in order to assure compatibility with patient anatomy. The device is also composed by end caps, lag screws,

threaded locking screw and an supplementary lag screw made all of stainless steel, aluminum alloy, carbon fiber, composite and plastic (85).

It is a class I, IIa and IIb non-absorbable and long-term surgically invasive implantable device manufactured by Orthofix S.r.l that has been CE marketed since 2018. CHIMAERA™ is intended for insertion into the medullary canal of a femur for the alignment, stabilization and fixation of various types of fractures of deformities. It is indicated for treatment of stable and unstable pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur alone or when these fractures occur in combination with shaft fractures extending distally to a point approximately 10cm proximal to the intercondylar notch. These include traumatic fractures, re-fractures, non-union, reconstruction, malunion, malalignment, pathological fratures, and impending pathological fractures (86).

The Use of the CHIMAERA™ is contraindicated for patients with general medical conditions not suitable for surgery, active or suspected latent infections in the fracture area and suspected or documented metal allergy or intolerance (86).

Through the use experience of CHIMAERA™, the following adverse effects are registered: delayed union or non-union of the fracture site; breakage of the device when subjected to the increased loading with delayed union and/or non-unions, conditions attributable to non union (osteoporosis, osteomalicia, diabetes, inhibited revascularization and poor bone formation causing loosening, bending, cracking, fracture of the device or premature loss of rigid fixation with the bone); mal-union of the bone and/or bending, cracking or even breakage of the device due to improper alignment; increased fibrous tissue response around the fracture site due to unstable comminuted fractures; early or late infection, both deep or superficial; thromboembolic events; fat embolism; avascular necrosis; shortening of the effected bone/fracture site; subclinical nerve damage due to the surgical trauma; material sensitivity reactions in patients following surgical implantation. Further details are provided in the IFU (17.2) (86).

CHIMAERA™ nail has not been evaluated for safety and compatibility in the Magnetic Resonance (MR) environment. It has not been tested for heating, migration, or image artifact in the MR environment. The safety of CHIMAERA™ nail in the MR environment is unknown. Scanning a patient who has this device may result in patient injury (85).

10.1.1 Intended purpose / Intended Use of the Investigational Device

In this study, the intended use of CHIMAERA™ is focused on adult patients that have been treated for of stable and unstable pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur alone or when these fractures occur in combination with shaft fractures extending distally to a point approximately 10cm proximal to the intercondylar notch.

The target population is broad, with no restrictions apart from those stated in the inclusion/exclusion criteria. Details on the routine intended purpose/use of CHIMAERA™ are provided in the IFU (17.2) (86).

10.2 Application of the device

The application of CHIMAERA™ has been performed according to routine clinical practice, without restrictions derived from patient participation in the study.

How to proceed in a particular surgery depends on the surgical requirements, where nails should be inserted depending on the bone to be treated, fracture severity, product knowdlege, the patient's condition and surgeon's experience. Details on the routine application of CHIMERA™ are provided in the IFU (17.2) (86).

For further information on CHIMAERA™ nail, please refer to the Operative Technique published in: https://abscdn.orthofix.it/resources/HF-1501-OPT-E0.pdf (85).

11. STUDY PROCEDURES

11.1 Description of Procedures

To ensure the observational nature of the study, all data will be collected if they are available in the patient's medical record. The degree of detail and completeness of data collected will therefore be dependent on the availability of data in medical charts and the routine clinical practice of the two participating sites. There are no Clinical Investigation Plan visits imposed, or procedures outside the usual clinical practice to guarantee that the study does not modify in any way the healthcare professional prescription habits or his/her healthcare practice. Unavailable data/assessments will be stated in the electronic Case Report Form (eCRF) as not available.

At the screening phase, only to patients who meet all inclusion and exclusion criteria the investigator will ask if he/she is willing to participate to the study and provide the Information sheet to the patient (and to the legal representative/guardian if applicable). Together with providing the Information sheet, the investigator (or an authorized designee) must also orally inform the patient (and the legal representative/guardian if applicable) about the objectives, procedures and duration of the study as well as the foreseeable risks and potential benefits deriving from participation in the same.

According to local legislation, it will be essential that before collecting any information from patient's 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.

Upon confirmation that the patient meets all the selection criteria, the physician participating in the study will proceed to extract the available study data (previously registered) in the patient's medical records.

The clinical benefit and the safety profile will be assessed since surgery within 12 months and until 6 months follow-up respectively after nail implant through the information collected from the medical records of the two participating sites.

All data, recorded in an electronic CRF, will be analyzed at the end of the study.

11.2 Study data collection

At the time of data collection, once the eligibility of patients has been confirmed, patients will be considered included and they will be assigned a permanent identification number so that the information managed does not contain personal data.

The procedures and data required are the following:

- Review of selection criteria and obtaining informed consent
- Sociodemographic characteristics (Age at surgery, gender, ethnicity)
- Anthropometric data (weight, height, Body Mass Index (BMI))
- Anamnesis data (worker, smoker, alcohol user)
- Relevant medical history (specifically related to other fractures that have occurred previously)
- Comorbidities (other acquired or congenital deformities)
- Clinical diagnosis: date of trauma, type and classification of fracture, cause of fracture, non-union, pathological fracture, results of RX diagnosis performed if available.
- Related surgery data:
  - Date of surgery
  - Femur-treated
  - Operation time
  - Antibiotic prophylaxis
  - CHIMAERA™ specification device (use of CHIMAERA™, nail composition, CCD angle, distal diameter, height and length of nail, type of lag screw, use of additional lag screw, distally lock of the nail, other synthetic media applied and device code)
  - Post-operative ADEs/SADEs and MDDs related to CHIMAERA™ (including blood loss)
  - Intraoperative fluoroscopy and time of fluoroscopy
  - Tip Apex Distance (TAD) calculation
  - Need of blood transfusion and number of blood bags used
  - Intraoperative measures (for corrections) (number of osteotomies, rotational correction, varus/valgus correction, shortening)
- Hospital stay data (date of hospital admission, date of hospital discharges, stay duration, presence of pain at the site of nail insertion)
- 1st follow up visit (Bone consolidation assessment data): date of assessment, fluoroscopy or RX performed, TAD calculation, bone consolidation/union (yes/no) by both observers, presence of pain at the site of nail insertion.
- 2nd follow up visit (): date of visit, presence of pain at the site of nail insertion.

- Last Follow-up visit (date of assessment, fluoroscopy or RX performed, TAD calculation, bone consolidation/union (yes/no) by both observers if not achieved in the last visit, presence of pain at the site of nail insertion.
- Reoperations (date, duration, post-operative x-ray, need of blood transfusion, intraoperative fluoroscopy and measures and main reasons of reoperation) performed within the 12 months after nail implant.
- ADEs/SADEs reported since the day of surgery until the last follow-up visit.
- MDDs reported since the day of surgery until the last follow-up visit.
- Concomitant medication prescribed since surgery until the last follow-up visit.

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

As this is a study based on primary use of data, safety monitoring and safety reporting, where there is a safety relevant result, will be provided on an aggregate level only, no reporting on an individual case level.

In studies based on primary use of data with a safety relevant result, reports of adverse events/adverse reactions will be summarized in the study report, i.e. the overall association between an exposure and an outcome will be presented. All Adverse Events (AEs) and device deficiencies will be collected and reported to the sponsor.

The following definitions are provided in accordance with MDR (EU) 2017/745 of the European Parliament and of the Council on medical devices (28) and its guidelines as MDCG 2020-10/1 (29) and ISO/DIS 14155:2020 (27).

12.1 Definitions

Adverse event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, symptom or medical condition (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device (MDR Article 2(57)).

a. This definition includes events that are anticipated as well as unanticipated events.

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved (MDCG 2020-10/1) (29).

Adverse Device Effect (ADE)

Any AE related to the use of an investigational medical device, including adverse events resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device and any event resulting from use error or from intentional misuse of the investigational medical device. (ISO 14155:2020).

Serious Adverse Event (SAE)

AE that led or could have led to any of the following:

a) Death,

b) Serious deterioration in the health of the patient, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment (MDR Article 2(58)

Serious Adverse Device Effect (SADE)

ADE that has resulted in any of the consequences characteristic of a serious adverse event (ISO 14155:2020).

Medical Device Deficiency (MDD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling (Article 2(59) of the MDR).

Unanticipated serious adverse device effect (USADE)

Any SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report and is therefore not included in the IFU (ISO 14155:2020).

Anticipated serious adverse device effect (ASADE)

SADE which by its nature, incidence, severity or outcome has been identified in the risk analysis report and is therefore included in the IFU (ISO 14155:2020).

12.2 Procedures for Reporting and Recording Adverse / Serious Adverse Events

Since this study is intended to collect safety information retrospectively related to the use of CHIMAERA™, the Investigators must record and document in detail all adverse events according to the designated eCRF page. All serious adverse events, whether or not deemed

investigational device related or expected, and all serious adverse device effects will be collected.

The following information on all AEs/SAEs will be recorded on the Adverse Event Form in the CRDe:

- Description of the event.
- Start and end dates.
- Maximum intensity reached.
- Causal relationship to the study device/procedure (unrelated, unlikely, possible, probable, causal relationship).
- Severity (yes/no).
- Actions taken in relation to the study product/device.
- Status of the event (resolved, resolved with sequelae, fatal, improved, ongoing, worsening, unknown).
- If serious: Severity criteria (death, life-threatening, hospitalisation or prolonged hospitalisation, permanent or significant disability, congenital anomaly, medically significant, transmission of infectious agent, serious injury or death due to device malfunction, medical or surgical intervention to prevent permanent damage).

As this is a non-interventional post-authorisation study, reporting of both serious and non-serious adverse events will not be required. In addition, as this is a retrospective study, adverse events are considered to have been previously reported. However, All SAEs will be reported to the sponsor through the SAE form and recorded into the safety database of the sponsor at the end of the study.

12.3 Assessment of causality

The relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

1. Not related.
2. Possible.
3. Probable.
4. Causal relationship,

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

1. Not related: Relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device.
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible.
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event.
- the event involves a body-site or an organ that cannot be affected by the device or procedure.
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors).
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar

devices and procedures.

- the event has a temporal relationship with investigational device use/application or procedures.
- the event involves a body-site or organ that:
    - the investigational device or procedures are applied to.
    - the investigational device or procedures have an effect on.
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known).
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible).
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out.
- harm to the subject is due to error in use.
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting as not delayed. Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

12.4 Assessment of expectedness

The assessment of expectedness of AEs related to the use of the investigational medical device will be made according to the expected risks described in the investigational plan and in the IFU.

13. STATISTICS

13.1 Statistical and Analytical Plans

Prior to any statistical analysis, a statistical analysis plan (SAP) shall be prepared and approved, which shall provide the technical details of the statistical analysis described below. Any deviation from the SAP shall be described and justified in the final study report.

All patients meeting the screening criteria will be included in the analysis, a list will be given of the patients removed from the analysis, as well as the reason for their removal. A general description of the variables included in the study will be provided. The distributions of absolute and relative frequencies for qualitative variables will be presented, as well as mean, standard deviation (SD), median, minimum and maximum for quantitative variables. If considered appropriate, 95% confidence intervals will also be presented. No imputation for missing data will be considered.

Analysis will be performed using IBM SPSS Vs 22.0. When an inferential analysis is required, parametric tests will be used for continuous variables and nonparametric tests in the case of ordinal or categorical or nonparametric variables. All hypothesis tests will be two-sided and with a significance level of 0.05. For variables not fitting a normal (or parametric) distribution, the Mann-Whitney test (for unpaired data) and the Wilcoxon test (paired data) will be used. Contingency tables and the comparison of proportions and/or frequency distributions will be analyzed using the chi-square test (or Fischer's exact test when appropriate) will be used.

13.1.1 Population(s) of analysis

The full analysis set (FAS) population consists of all patients included in the study after selection criteria review. The full analysis set will be used for all raw data listings.

The clinical benefit population consists of patients who have available data that allow the primary efficacy endpoint assessment.

The safety population includes all adult patients in whom CHIMAERA™ has been used.

13.1.2 Efficacy, Safety and Other Variables

13.1.2.1 Efficacy Variables

The clinical benefit of CHIMAERA™ will be assessed by the percentage of patients in which bone union has been achieved within 12 months from the nail implant.

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.
- Patient with fractures on the upper limbs not caused by the CHIMAERA™ (e.g. simply stumbled or had a car accident)
- Patient underwent reoperation after first bone union evaluation.
- Patient who has not suffered contralateral leg fracture.
- Patient in whom no refraction occurred where the nail was applied.

A double evaluation will be required (observer 1 and observer 2). Only if both evaluations are positive, the treatment goal will be considered achieved.

13.1.2.2 Safety Variables

The safety profile of CHIMAERA™ will be assessed through the percentage of patients that required a reoperation (i.e., additional surgery) caused by at least one of the following safety events:

- Expected or unexpected adverse effect potentially or certainly related to the CHIMAERA™ (Adverse Device Effects (ADEs)/Serious Adverse Device Effects (SADEs)) since the nail application until 6 months follow-up after nail implant.
- Medical Device Deficiency (MDDs) (i.e., breaking, loosening, or bending of the nail or of the screws) that caused an effect on the patient since the nail application until 6 months follow-up after nail implant.

All the reoperations that have occurred are considered but also those that have not occurred but that could have occurred (e.g., a patient who had a cut out but for any reasons has not been operated). It should be considered also all ADE/SADE/MDD that could have caused an additional operation.

13.1.3 Statistical Evaluation

13.1.3.1 Evaluation of Efficacy

Evaluation of efficacy will be performed through the analysis of the primary objective of this study: 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.

. It is required a double evaluation with two positive opinions from both observers (observer 1 and observer 2) to consider the treatment goal achieved.

For this objective, descriptive statistics of the number and percentage of patients in which bone union was achieved will be provided both as continuous and categorical variables. The 95% CI will also be presented.

13.1.3.2 Evaluation of Safety

The evaluation of safety will be performed through the analysis of the secondary objective of the study: 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” which includes all patients who have undergone an intramedullary nailing technique with the CHIMAERA™ medical device.

The number and percentage of patients that required a reoperation due to at least one ADE/SADE/MDD will be calculated with a 95% confidence interval (CI). An analysis will be carried out according to degree of severity, seriousness, and relationship with the medical device.

All the reoperations that have occurred are considered but also those that have not occurred but that could have occurred (e.g., a patient who had a cut out but for any reasons has not been operated). It should be considered also all ADE/SADE/MDD that could have caused an additional operation. Therefore, the number and percentage of patients that hypothetically would have caused a reoperation due to at least one safety event will be described and calculated with a 95% CI.

13.2 Determination of the Sample Size

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 which bone union rate was achieved is 98.3% (IC95% 93%-100%) (1-26). 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 2. 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 were chosen.

13.3 Changes in the Conduct of the Study or the Planned Analyses

As this is a retrospective study with a clearly defined population, no changes are expected either in the conduct of the study or in the planned analyses.

13.4 Statistical and Analytical Issues

No adjustment for multiple comparisons will be performed.

13.4.1 Handling of Dropouts or Missing Data

The number of observations (N) and missing data (N missing) will be specified. There is no plan to impute missing data.

13.4.2 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.

14. ETHICS AND REGULATORY REQUIREMENTS

14.1 Approval

The study complies with the basic ethical principles contained in the (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), the World Medical Association's Declaration of Helsinki on the ethical principles for medical research involving human subjects (87), and subsequent amendments.

The study will be submitted for evaluation by an accredited Independent Ethics Committee/ Institutional Review Board (IEC/IRB), where applicable.

This study will be conducted according to the procedures described in this CIP, with the Ministerial Decree 30 November 2021 “Misure volte a facilitare e sostenere la realizzazione degli studi clinici di medicinali senza scopo di lucro e degli studi osservazionali e a disciplinare la cessione di dati e risultati di sperimentazioni senza scopo di lucro a fini registrativi, ai sensi dell’art. 1, comma 1, lettera c), del decreto legislativo 14 maggio 2019, n. 52”, where applicable, with the guideline of the Italian National coordination centre of local ethics committees for clinical trials concerning medicinal products for human use and medical devices issued on 26 July 2022 – Version n. 1 (88), and the Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices (28) and its guidelines as MDCG 2020-10/1 (29) and ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice (27).

In addition, the study complies with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (89) and with the Legislative Decree 10 August 2018, n. 101 “Disposizioni per l'adeguamento della normativa nazionale alle disposizioni del regolamento (UE) 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonche' alla libera circolazione di tali dati e che abroga la direttiva 95/46/CE (regolamento generale sulla protezione dei dati)” (90).

It will be also conducted in compliance with this Clinical Investigation Plan, Standard Operating Procedures (SOPs) and referred to ISO 14155 where applicable and with local laws and regulations relevant to the research of medical devices in the country of conduct.

By signing the CIP, the investigator agrees to adhere to the instructions and procedures described in the CIP and thereby to adhere to the principles of good clinical practice that it conforms to.

The sponsor will submit the pertinent documentation to the ethics committee and applicable regulatory agency. The study must not be started until their approval has been obtained. Any amendment changing the risk-benefit relationship for the patient must, after signature by the sponsor, be submitted for evaluation by the ethics committee and applicable regulatory agency for approval.

The study staff involved in the conduct of this clinical investigation will have appropriately qualified training and experience to perform the assigned tasks.

14.2 Subject Information and Consent

Patients will be identified via an existing database held by the Primary care team. A member of the primary care team will invite the patient to be part of the study. This invitation may be in person at an existing standard of care follow up appointment or via the post. Each patient who is invited to participate in the study will be provided with an information sheet in which the

study objectives, methods, planned duration, the number of participating patients, the expected benefits and potential risks will be explained in detail. This document will be written with a vocabulary that allows its content to be completely readable and understandable for the patient. Patients will also be explained that they are free to refuse to participate in the study and to withdraw from the study at any time without it affecting their future treatment and medical care.

The willingness of the patient to participate in the study will be documented in writing in a consent form. The patient or legal representative will sign the informed consent form indicating the date of signature. A legal representative signature will be requested if the subject is legally incapable, or is incapable of making decisions or his/her physical or mental state does not allow him/her to take charge of his/her situation, or an impartial witness if the subject or his/her legal representatives cannot read. Each investigator will keep the original consent documents and give a copy to the patients. In the case of deceased patients, the ethics committee may waive the need for consent.

Patients may revoke at any time their consent to continue participating in the study and for use of their data in the analysis.

14.3 Subject Confidentiality

The information disclosed and obtained during this study will be considered confidential and must be treated as such at all times.

The study sponsor and investigators should ensure the confidentiality of the subjects' data and that the study complies at all times with the Legislative Decree 10 August 2018, n. 101 "Disposizioni per l'adeguamento della normativa nazionale alle disposizioni del regolamento (UE) 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonche' alla libera circolazione di tali dati e che abroga la direttiva 95/46/CE (regolamento generale sulla protezione dei dati)" (90). This Law is the adaptation of the Italy legal system of the Regulation (EU) 2016/679 of the European Parliament and the Council, on 26 April 2016, GDPR first implemented on 25 May 2018 (89).

For this purpose, each patient recruited for the study will be assigned a unique subject identification number. This means that the names of the participating patients are not included in the study data sets that are transmitted to promotor sites, and that in no study document or material will patients be identified by their name but only by an identification number.

In compliance with current legislation on data protection, when the treating physician receives a request for the exercise of rights from a patient included in the study, he/she must verify the ownership of the data by means of a legal document (ID card, driving license) and proceed to contact the sponsor by e-mail or by post to the attention of the Data Protection Delegate (DPD), without disclosing in any case the patient's personal data, but indicating only the code to which the holder corresponds, the code of the study and the code of the study site; as well as the right that the patient has been asked to exercise. The physician should not send to the

sponsor or any of its delegate the document proving the identity, since it was verified by him at the time of the request. The sponsor or its possible DPD will manage the request and will issue an answer according to the case.

All materials, information (oral or written) and unpublished documentation provided to the investigator, including this Clinical Investigation Plan and the CRFs, will be considered the property of the sponsor. The study data and materials may not be disclosed in part or in full by the investigator or his/her staff to any unauthorized person without the prior formal written consent of the sponsor.

The study database and the CRF will be coded and protected from nonpermitted uses by persons unrelated to the research and, therefore, will be considered strictly confidential and will not be disclosed to third parties. However, the study data must be available for inspection upon request by the regulatory authorities, ethics committees and the sponsor (or its representatives), as appropriate.

The data generated by the study must be available for inspection upon request by representatives of the national and local health authorities, monitors of the marketing authorization holder, representatives and collaborators of the sponsor, and the IEC/IRB of each study site, as appropriate.

Only medical history data that are related to the study will be subject to verification. This verification will be done to the extent possible in the presence of the principal investigator/coinvestigators, and the confidentiality of all personal data of the subjects participating in the clinical investigation will be maintained at all times in accordance with the EU data protection regulation.

Regarding the eCRF, each investigator will be given a sealed document with a username and a password of between 4 to 6 digits. These codes will be considered confidential and nontransferable and are subject to the same confidentiality requirements as the rest of the documents, including the Clinical Investigation Plan. The investigators are responsible for keeping their passwords secret and not disclosing them to third parties. The study sponsor and its representatives will have access codes permitting only read-only access to eCRFs, but at no time will they be able to modify the information entered by the investigators.

14.4 Informing the General Practitioner

Given that the proposed research project has a post authorization observational retrospective design, no type of diagnostic or therapeutic intervention outside of routine clinical practice were applied. It involves collection of data from the medical history of selected patients in whom a specific therapeutic strategic has already been assigned based on routine practice, without interference with the physician’s prescription habits.

15. STUDY MANAGEMENT AND ADMINISTRATION

15.1 Monitoring

Authorized, qualified representatives of the Sponsor or designated personnel of a Contract Research Organization (CRO) may visit investigational sites in regular intervals as defined in the monitoring guidelines to verify adherence to Clinical Investigation Plan and local legal requirements, to perform source data verification and to assist the Investigator in his/her study related activities.

15.2 Direct Access to Source Data/Documents

15.2.1 Source Documents

A source document is an original or certified copy of printed, optical, or electronic document containing source data, where documented data are recorded for the first time. Examples of source documents include hospital records, laboratory notes, physician reports, appointment books, and records kept at the investigation site, laboratories, and medico-technical departments involved in the clinical investigation.

15.2.2 Source Data

Source data are all information in original records, certified copies of original records of clinical findings, observations, or other activities, necessary for the reconstruction and evaluation of this retrospective observational study. These also include electronic source data initially recorded in an electronic format. The data source will be the medical records on both participating study sites, including medical charts.

15.2.3 Direct Access

Direct access is defined as the permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of this retrospective observational study.

15.2.4 Permission of Access

The investigator will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections, providing direct access to primary patient data (i.e. source data) which supports the data on the eCRFs for the study, e.g. general practice charts, hospital notes, appointment books, original laboratory records.

Any party (e.g. domestic and foreign regulatory authorities, the sponsor and/or authorized representatives of the sponsor such as monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

15.3 Audit and Inspection

The competent health authorities, within the scope of their competences, will verify compliance with the legal requirement related to post-authorization studies conducted in Italy through the pertinent inspections and according to the procedures that may be established.

Inspections will be carried out before, during, or after the conduct of the study by duly qualified inspectors. Inspections may be performed in sites related to the conduct of the study and, among others, at the research site or healthcare sites where the study is conducted, at any analytical laboratory or diagnostic center used, at the facilities of the sponsor and/or contract research organizations or companies involved in the conduct of the study, and at the IEC/IRB which evaluated the study.

15.4 Patient Data collection

All study data will be collected from the patient's medical history during scheduled visits according to local clinical practice for patient´s disease follow-up. The investigator or designated site staff will be solely responsible for entering the data in the CRF and must ensure the data recorded in the CRF are legible, accurate and complete, and within the established time period.

Data recording will be performed through an eCRF. The data received using the e-Clinical methodology will be submitted to the appropriate work procedures to comply with the FDA 21 CFR Part 11 regulation, which ensures that the data received via electronic transmission are as valid as the originals received on paper. This regulation establishes the rules for the use of electronic data and defines the requirements of all the systems for collection, storage, maintenance and security of the data. An automatic validation program will check for data discrepancies, thus allowing modification or verification of the data entered by the investigator or designated person.

15.5 Adherence to Clinical Investigation Plan

By signing the Clinical Investigation Plan, the investigator agrees to adhere to the instructions and procedures described in the Clinical Investigation Plan and thereby to adhere to the principles of good clinical practice that it conforms to.

15.6 Investigator Site File

The documentation related to the study comprises the study file and will consist of the essential documents that allow evaluation of its conduct and the quality of the data obtained. These documents demonstrate compliance by the investigator and the sponsor of the requirements established for the study.

The master study file will provide the basis for the audits that may be performed by the sponsor through independent auditors and for inspections by the competent authorities.

The sponsor and the investigator will retain the essential study documents and materials for the time required by currently applicable legislation after completion of the study, or during a longer period if provided by other applicable requirements.

The essential documents and materials must be filed so they can be made readily available to the competent authorities if requested.

The sponsor will designate the persons of its organization responsible for the study files and access to the files must be restricted to designated persons.

The media used for storage of the essential documents must ensure that the document and materials remain complete and readable for the expected storage period and that they can be made readily available to the competent authorities if requested. Any changes to the records must be traceable, allowing the original and corrected entry to be known, as well as the date and signature of the author of the change.

15.7 Data Handling

15.7.1 Data management

The patients included in the study will be identified only by a numerical code, such a way that no personally identifiable patient data will be collected in the sponsor's study database. Thus, the sponsor will work with pseudonymized (coded) data. The pseudonymization procedure will be carried out by the study investigator, who will create a list in which the patients' personal data will be related to the codes assigned by the sponsor that will identify the patient during the study. This list will be kept at the study site and in the investigator's file at all times.

When the database is closed, it will be transferred to Evidenze Health España S.L, for debugging and analysis. Once the study is finished, the database will be transferred to the sponsor as its owner.

For the development of the proposed study, both the Data Controller and the Data Processor undertake that the present research will be carried out using health data obtained in routine medical practice and/or previous research, always under the current legislation at the time they were collected; and that they have been pseudonymized for further processing. The recorded information is encrypted for its transfer to the study database.

The teams in charge of performing the pseudonymization are technically and functionally independent of the researchers who have collected the data, so re-identification and unauthorized access by third parties is not possible. This is broken down according to the following organization:

- Research team: corresponds to the healthcare team delegated to the study with direct access to the patients' original data and knowledge of their identity. These personnel are hired and perform their functions at the health site where the study is carried out and have no direct or indirect contact or relationship with the personnel responsible for

programming the eCRD, a system designed to automatically perform pseudonymization when a patient is included in the study.

- IT technical team: corresponds to Orthofix S.r.l IT department, whose functions include the programming of the CRDs contracted by the clients. This staff is composed of IT programmers with exclusive training in the area. Their physical offices are located in the company's facilities, and they have no contact of any kind (direct or indirect) with the research team. The Orthofix S.r.l Project manager of the study is the internal responsible in the company for the verification of the user requirements foreseen in the system, and this role (CTL) corresponds to the sponsor operations department. This implies that between the research team located in the health study site and the sponsor team of programmers there is no possibility of communication since they do not participate, cooperate, or relate to each other for any phase of the development of the system or later once the data entry begins.

Likewise, a daily, weekly and monthly backup of all servers that keep the pseudonymized data is performed. All computer equipment has antivirus protection, firewalls, controlled access, permanent surveillance, alarms, in addition to other relevant security measures to ensure that the information is protected against attacks and accidental losses. In case of serious security breaches, Orthofix S.r.l Data protection officer or its possible DPD will notify the corresponding entities within 72 hours.

On the other hand, Orthofix S.r.l, through its Data Protection Delegate, states that it has conducted an impact assessment to determine the risks arising from the processing of health research data foreseen in the study, and technical and organizational measures have been taken according to the levels of risk detected.

15.7.2 Quality assurance

The data generated by this study may be reviewed by the sponsor (or its representatives), the competent health authorities and the ethics committees of each site, as appropriate. Therefore, the investigator and the site will ensure the sponsor or its representative (including the monitor), the ethics committee and the competent authorities have access to the study documents.

Any discrepancies detected requiring resolution will be corrected by authorized study site staff. Data clarification requests may be created describing the nature of the problem and requesting clarification of all other discrepancies and missing values and sent to the research site. The designated staff of the research site must respond to the clarification request and confirm or correct the data. Once these actions have been completed and the database has been declared complete and correct, database closure will be performed, and the data will be available for analysis.

15.8 Clinical Study Report

The sponsor will notify the end of the study according to the Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices (28), and its guidelines as MDCG 2020-10/1 (29) and local regulations. The end of the study is defined as all close out visits and database lock performed.

The sponsor will also notify any temporary halt of the study or the premature end of the study, including the reason for such an action, as per the Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices (28), and its guidelines as MDCG 2020-10/1 (29) and local regulations.

Irrespective of the outcome of the retrospective observational study, the sponsor shall submit to the member states in which a clinical investigation was conducted a clinical investigation report, accompanied by a summary presented in terms that are easily understandable to the intended user, within the timelines laid down in the Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices (28) and its guidelines as MDCG 2020-10/1 (29) and local regulations.

15.9 Archiving and Data Retention

Essential documents are to be retained for the periods required by applicable national and international legislation but not less than 15 years after routine/premature termination of a clinical study.

The final report shall be retained for at least 2 years after the Investigational devices are removed from the last market.

15.10 Allocation of Responsibilities

The responsibilities of the Investigator, Monitor and Sponsor of the clinical study as regards handling of data, storage of data, planning, assessment and quality assurance are regulated by ISO 14155-1 “Clinical investigation of medical devices for human subjects — Good clinical practice” (27).

15.11 Financial Disclosure

Orthofix S.r.l will provide funding for the study according to the guidelines of the present clinical investigation plan. This funding includes all materials required for the conduct of the study, the cost of the processes of authorization and control before the IEC/IRB and health authorities, the design, maintenance and management of the database and statistical analysis of the information generated. Funding will be completely independent of the study results.

Given that this is an observational study according to routine clinical practice conditions, its conduct will not entail any extra expense for the site other than the dedication of the investigator to complete the information required in the eCRF. In any case, the study sponsor

will have a financial schedule of the study that will be available for consultation whenever it should be necessary.

15.12 Disclosure of Clinical study Information and publication

The Sponsor and all Investigators shall agree on the final study report. A publication of the results of the study in a scientific journal is intended.

Results may also be used in submissions to regulatory authorities. The following conditions aim to protect commercial confidential materials (patents etc.), rather than restrict publication.

All information concerning CHIMAERA™ (such as patent applications, technical drawings, manufacturing processes, basic scientific data supplied to the Investigator by the Sponsor and not previously published) is considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees not to use it for other purposes without the Sponsor's written consent.

It is understood by the Investigator that the Sponsor will use the information developed in this clinical study in connection with the development of CHIMAERA™ and therefore may be disclosed as required to other Investigators or any appropriate international Regulatory Authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this study.

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17. APPENDICES

17.1 CASE REPORT FORM

Attached as a separate document.

17.2 Instructions for Use (ORTHOFIX CHIMAERA HIP FRACTURE SYSTEM – TROCHANTERIC NAILING SYSTEM ™)

Attached as a separate document.

17.3 IEC/IRB AGREEMENT

Attached as a separate document.

17.4 FINANCIAL SCHEDULE

Attached as a separate document.

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