PROTOCOL

CLINICAL INVESTIGATION WITH MEDICAL DEVICE

Title of the Clinical Investigation:	*Observational, prospective, and multicenter clinical investigation for the evaluation of clinical parameters in elderly patients with proximal femoral fracture treated with the Chimaera intramedullary nail (Orthofix Srl).*
Clinical Investigation Identification Code:	*OCI_1901*
Protocol Version Number:	*02*
Date of Issue:	*14/10/2019*
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APPROVAL OF THE PROTOCOL

Investigators:

- approve this Protocol;
- declare that the clinical investigation will be conducted in accordance with Good Clinical Practice, the UNI EN ISO 14155:2012 Standard and according to the provisions of this protocol.

_____	_____
Dr. Roberto Civinini	Date
_____	_____
Dr. Giovanni Benelli	Date
_____	_____
Dr. Pier Giulio Davini	Date
_____	_____
Dr. Andrea Pizzoli	Date
_____	_____
Dr. Alberto Momoli	Date
_____	_____
Dr. Gaetano Bruno	Date
_____	_____
Dr. Giacomo Papotto	Date
_____	_____
Dr. Nicola Tartaglia	Date

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1 Medical Device Information

1.1 Identification on the medical device

The medical device subject to this clinical investigation is the:

"Chimaera ™ Hip Fracture System – Trochanteric Nailing system", di hereinafter (Chimaera).

Chimaera is a trochanteric nail system classified as a class IIb medical device, manufactured and marketed by Orthofix Srl on the markets of the European Union and some markets outside the European Union starting from 02 May 2016.

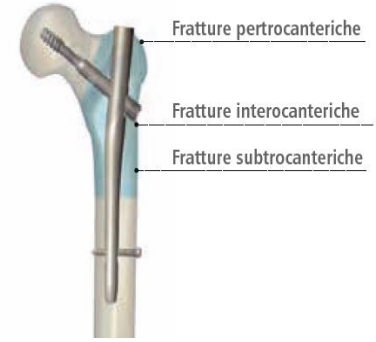
Note:

In the present clinical investigation, only patients treated with nails with a length of 180 mm, hereinafter referred to as "short nail", will be observed.

1.2 Intended use

The Chimaera *Trochanteric Nail System* was developed for insertion into the intramedullary canal of the femur for the purpose of aligning, stabilizing, and fixing various types of fractures or deformations of the proximal femur in an adult population.

Chimaera is indicated for the treatment of fractures located in the pertrochanteric, intertrochanteric and subtrochanteric region of the femur, stable or unstable, or in combination with diaphyseal fractures extending distal up to 10 cm from the intercondylar fossa.



Note:
in accordance with the patient selection criteria, pertrochanteric, intertrochanteric and subtrochanteric fractures of the femur, which are treatable with the short version of the nail, will be observed during this clinical investigation, while diaphysiar fractures that should be treated with the long version of the nail will be excluded from the present clinical investigation.

The Chimaera has been designed for professional use only. Surgeons responsible for supervising the use of the product must possess a thorough understanding of orthopedic fixation procedures and must be familiar with the devices, instruments, and surgical procedure, including application and removal.

For further details please refer to the package insert "Instructions for use" published on: http://abs.orthofix.it/db/resources/PQ_HFN.pdf

1.3 Detailed description of the device

The *Chimaera* is a system consisting of:

- Canulated intramedullary nails in titanium alloy, of various lengths and diameters.
  In the present clinical investigation, only patients treated with nails of 180 mm length, hereinafter referred to as "short nail", with a proximal diameter of 15.5 mm and a distal diameter of 10 or 11 mm (Figure 1), with anatomical curvature that allows insertion into both the right and left femur, will be observed. For this reason, diaphysiarial fractures that can be treated with the long version of the nail, in accordance with the patient selection criteria, are excluded from the present clinical investigation.

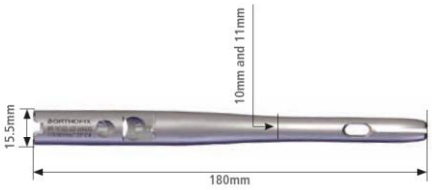


Figure 1: Technical characteristics of the short nail

Figure 2: Handle for inserting the nail

The proximal part of the nail has a threaded hole that allows the nail to be connected to the handle by means of a locking tie-rod. The handle required for nail insertion (Figure 2) consists of a radiolucent carbon fiber structure with steel connection elements and has locking holes for some components of the insertion instrumentation such as guide wire guides, trocars, reamers and screwdrivers.

The proximal part of the nail also has two holes designed to allow the insertion of one or two cephalic screws: depending on the desired cervical-diaphyseal angle (CCD), there are two distinct versions of the short nail with proximal holes at 125° or 130° (Figure 3).

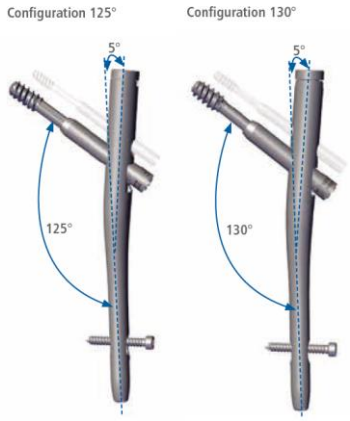


Figure 3: angles of the main and additional cephalic screw.

The distal tip of the nail has a tuning fork designed to lower the pressure exerted by the nail on the cortical of the femur and thus decrease the likelihood of peri-implantation fractures occurring.

- A mandatory main cephalic screw required for proximal nail locking to the femur (Figure 4) and an optional supplemental cephalic screw (Figure 5) to counteract rotational instability of the bone abutments where necessary.

Figure 4: Main Cephalic Screw

Figure 5: Secondary Cephalic Screw (Optional)

Both cephalic screws are marketed in telescopic (sliding) or fixed-length versions. In the present clinical investigation, only patients treated with telescopic screws designed to allow the fracture to compact and thus lower the probability that the screw protrudes from the head of the femur (serious complication called *cut out*) will be observed.
Both cephalic screws are also self-locking on the housing hole positioned on the head of the nail: this feature lowers the probability that the screws protrude laterally.

- Threaded screws for distal locking of the nail (Figure 6), which can be done with 3 different options, i.e. static, dynamic or static and potentially dynamizable later (Figure 7).

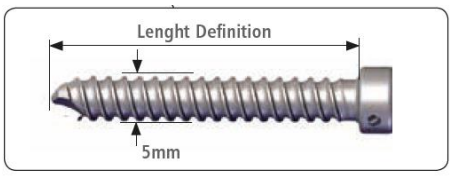


Figure 6: Distal Threaded Screw

Figure 7: Different Options for Distal Locking

- Blanking plugs at different protrusion levels to be inserted into the nail head (Figure 8).

Figure 8: Blanking caps

- Instruments for inserting (Figure 9) and removing (Figure 10) the nail.

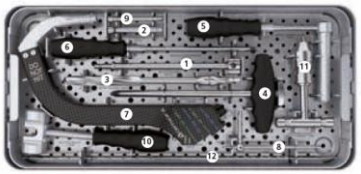


Figure 9: Insertion tools

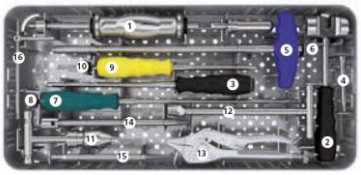
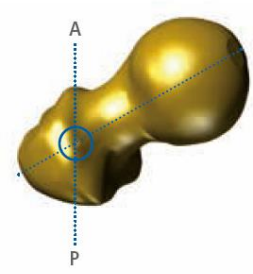


Figure 10: Nail removal tools

For further details regarding the components of the *Chimaera system*, please refer to the surgical technique published on: http://abs.orthofix.it/db/resources/HF-1501-OPT-I1.pdf.

1.4 Surgical procedure related to the use of the medical device.



The nails of the *Chimaera system* are inserted with anterograde access: the insertion point varies with the anatomy of each patient and generally coincides with the apex of the greater trochanter (Figure 11) or is slightly shifted to a more medial position.

Figure 11: Nail insertion point.

The insertion of the nail (Figure 12) is performed with the patient placed in a supine position with the help of a series of instruments according to the following macro-phases:

- Opening the insertion point.
- Bore of the medullary canal.
- Nail insertion.
- Proximal locking with one or two cephalic screws.
- Distal locking.
- Inserting the cap.

Figure 12: Short nail inserted and secured using 2 proximal screws and 1 distal screw.

For more details about the components of the *Chimaera system*, please refer to the surgical technique published on: http://abs.orthofix.it/db/resources/HF-1501-OPT-I1.pdf.

1.5 Indications for the traceability of the medical device.

The use of the *Chimaera* is already part of the normal clinical practice of the centers involved, so this device is not to be considered an experimental product. For this reason, the supply and traceability of the *Chimaera* at the centers involved will follow the standard commercial process of supplying medical devices.

2 Literature Analysis (Background)

Proximal femur fracture, commonly known as hip fracture, is one of the most frequent and serious injuries that can occur in elderly individuals.

They are classified into three types depending on the location: a) intracapsular fractures of the femoral neck (about 45% of PFFs); b) extracapsular fractures in the intertrochanteric region (about 45%); c) subtrochanteric

fractures (located between the lesser trochanter and the femoral isthmus, about 10%).[1] The distinction between intracapsular and extracapsular is important, because it addresses the likelihood of vascular impairment. Intracapsular fractures can damage the head of the small femur with the risk of avascular necrosis and/or non-union, or the management of these fractures. Extracapsular fractures (intertrochanteric or subtrochanteric) carry a minimal risk of vascular impairment, and their treatment focuses on anatomical reduction and stabilization with implants (such as nails or plates) to allow for early mobilization and loading during fracture healing.[2]

Hip fracture continues to be the most common injury in the elderly population. The incidence appears particularly high over the age of 75, when both the prevalence of osteoporosis increases (more than 45% for women, more than 18% for men) and the risk of falls and, therefore, often even low-energy trauma is sufficient to cause the rupture of the proximal portion of the femur. By 2050, the proportion of the world's population over 60 years of age will almost double from 12% to 22%, and the annual incidence of proximal femur fractures worldwide will increase proportionately to 6.26 million.[3]

Hip fracture is now considered one of the major social and health emergencies in the geriatric field. Despite recent significant improvements in the field of surgery and rehabilitation, hip fracture remains a difficult challenge for patients, their families, and orthopedic surgeons. In fact, these fractures often have a strong impact on the patient's mobility and therefore on the performance of activities of daily living. All this translates into a dramatic deterioration in quality of life with a significantly reduced life expectancy.

In fact, about 10% of patients over 75 years of age who suffer a hip fracture die within 30 days of surgery at cause of intra- and post-operative complications that aggravate a general state of health already compromised by pre-existing comorbidities. In addition, the drastic change in life triggered by the severe disability caused by this fracture, which often leads to a substantial loss of autonomy, causes the 1-year mortality rate to rise between 14% and 36%.[5] 42% of survivors do not return to pre-fracture mobility, 35% are unable to walk independently, 20% are unable to shop independently, and approximately 20% enter a long-term care facility during the first year after a fracture.[4]

In an attempt to lengthen the expectations and quality of life of these patients, the most recent guidelines suggest a multidisciplinary approach for the treatment of unstable hip fractures that involves, where possible, the close collaboration of different specialists such as the orthopedist, the geriatrician, the anesthesiologist, the cardiologist and the physiatrist. Although a consensus on the best possible treatment has not yet been found, several studies demonstrate a real benefit in the use of multidisciplinary protocols that always provide for timely surgical treatment of the fracture.[5.6]

To date, there are several treatment options available for unstable hip fractures, each with advantages and disadvantages, including external fixation systems, internal fixation systems and partial or total hip replacement. In the field of internal fixation, the use of intramedullary nails has become increasingly popular due to the biomechanical advantages they provide in many indications compared to other synthetic media such as plates or dynamic cephalic screws.

However, the percentage of complications considered serious, i.e. requiring reoperation, associated with intramedullary nail treatment, such as cut-out, lateral protrusion of the cephalic screw and peri-implantation fractures, remains clinically significant (overall they can affect up to 30% of patients treated).

The *Chimaera* developed by Orthofix Srl is an intramedullary nail also indicated for the treatment of proximal femur fractures that integrates technical features specifically designed to decrease the probability of encountering the most serious and frequent complications in this type of treatment.

These technical characteristics are: a) the double telescopic cephalic screw, designed to counteract the rotational instability of the bone stumps and allow the compacting of the fracture, lowers the probability of cut out; b) the locking mechanism of the cephalic screws on the nail lowers the probability that the screws

protrude laterally; c) the tuning fork positioned on the distal tip of the nail, designed to lower the pressure exerted by the device on the cortical femur, decreases the likelihood of peri-implantation fractures.

3 Rationale for clinical investigation

Orthofix Srl has developed and placed on the European market the Chimaera after carrying out an evaluation of the clinical performance and safety of the medical device on the basis of biomechanical tests and clinical data obtained from scientific publications on equivalent products (on request, more details available in Technical File A.1.10 archived at the Sponsor).

The outcome of this pre-market assessment established that the Chimaera meets the necessary requirements for CE marking, in particular it has an acceptable risk/benefit ratio when used according to the manufacturer's indications for use.

To date, more than 3000 treatments have been carried out in Europe with Chimaera: the frequencies of serious complications received by Orthofix Srl through the passive medical device vigilance system are lower than those reported in the literature for equivalent nails on the market for several years. This first evidence seems to confirm the efficacy and safety of the technical characteristics integrated into the device; however it must be integrated with clinical data collected and analyzed with the methodology of a clinical investigation.

The data obtained from this Clinical Investigation will be used to complement the pre-market clinical evaluation carried out on the Chimaera with post-market clinical data from the use of the device in a representative number of patients and users observed in normal clinical practice.

4 Ethical considerations

The contents of this Protocol comply with the recognized ethical principles for clinical trials, the principles of good clinical practice (ICH-GCP Guidelines) on clinical investigations with medical devices and the applicable regulations (UNI EN ISO 14155).

The procedures described in this Protocol are part of the normal clinical practice of the Centers involved. In fact, this clinical investigation is observational so it will not change the clinical protocols currently in use in the Centers involved, nor does it involve additional risks for patients and investigators.

Participation in research is free, not bound by interests and motivated by a spontaneous collaborative contribution to acquire data of common interest. There is no direct compensation for physicians participating in this Clinical Investigation.

The Investigator in charge of each Site shall ensure that this Clinical Investigation is conducted in accordance with the Declaration of Helsinki and with national and international laws and regulations that ensure the greatest possible protection for the patient.

The procedures described in this Protocol will be applied only after the evaluation and possible approval of the contents by the relevant Ethics Committees of each participating Center.

The physician's decision to treat a patient with Chimaera is entirely independent of the patient's willingness to participate or not participate in the Clinical Investigation, i.e., the physician will make such a decision solely based on his or her own medical considerations in the best interests of the patient before seeking consent to participate in the Clinical Investigation. Only after the physician has decided to treat a patient with Chimaera will he ask the eligible patient for consent to participate in the Clinical Investigation and verify the inclusion and exclusion criteria. It is understood that such a patient will receive the same type of treatment and all related care even if he or she decides not to participate in the Clinical Investigation or is not eligible to participate.

Before enrolling the first patient, each Investigator will also be adequately instructed by Orthofix Srl on the contents of this protocol, the use of the electronic system that will be used for data collection and the procedures of the clinical investigation.

4.1 Identification of subjects and confidentiality

The Investigator will assign a unique, predefined and sequential code to each enrolled patient. Only the Investigator will be able to associate this code with the patient's name for communications relating to the Clinical Investigation or for the compilation of the data collection form, therefore the pseudo-anonymization of the patient will be guaranteed.

As stated in the informed consent form, the confidentiality of patient data will be always maintained. Each patient (or his/her legal representative) will be informed by the Investigator that his/her clinical documentation may be audited by the Sponsor's representatives (monitor) or by regulatory authorities.

Each patient, at the same time as signing the consent for participation in the Clinical Investigation, will also be asked to sign for the collection and processing of clinical data that will be collected without direct identifiers and will be reprocessed anonymously. In addition, security measures will be applied appropriate to the type of data and the type of processing, in accordance with the requirements of GDPR 679/2016 and in compliance with the Guidelines for the processing of personal data in the context of clinical trials of medicinal products – 24 July 2008 (Official Gazette no. 190 of 14 August 2008).

Finally, patients will be able to exercise the rights referred to in European Regulation no. 679/2016 art. 7 of the Privacy Code (e.g. access your personal data, integrate them, update them, rectify them, limit them, oppose processing for legitimate reasons, request their portability, etc.) by contacting the Site directly or, through it, the Promoter. Furthermore, no further data concerning the patient will be collected, without prejudice to the use of any data already collected to determine, without altering them, the results of the clinical investigation.

4.2 How to obtain informed consent

Note:

An adult patient with previously untreated proximal femur fracture who, based on the free judgment of the Investigator, will have a regular indication for surgical treatment with Chimaera will be considered eligible for participation in the clinical investigation.

4.2.1 Patients able to give consent personally

Before taking part in the Clinical Investigation, any eligible patient capable of expressing valid consent personally, understood to be of sound mind and willing and able to affix his/her signature and date on the form:

1. You will be informed of the possibility, voluntary, of participating in the clinical investigation and that, if you agree to participate, you may refuse to continue the investigation at any time without prejudice to subsequent treatment;
2. will be informed about the potential benefits for the scientific community and for other patients deriving from the increase in the scientific knowledge generated by the survey;
3. if interested, through a specific information notice you will receive adequate information on the purpose of the clinical investigation, its characteristics (observational and non-interventional), the schedule of visits, the expected duration of the same, your responsibilities and the methods of collecting and processing clinical data;
4. he/she will be given the necessary time to receive from the Investigator all clarifications and additional information he/she deems necessary;
5. if he decides to participate in the clinical investigation, before carrying out the first visit provided for by the Protocol, he will sign and give the informed consent of which he will keep a copy.

It is understood that:

- as specified in the form for obtaining consent, by signing, the patient expresses his/her consent both for participation in the survey and for the collection and processing of clinical data;
- if deemed necessary in the best interest of the patient's health, the Investigator may decide to discontinue participation in the investigation without the consent of the patient who will be informed of the decision and the related reasons.

4.2.2 Patients unable to give consent personally

For patients unable to express valid consent personally, consent will be obtained in the same way as for patients able to express consent, but through a respondent (witness, legal guardian or family member/cohabitant of the patient) who will act on behalf of the patient according to the following cases:

a) If a patient is of sound mind and verbal consent but is temporarily unable to sign and date the consent form in his or her own hand, for example due to a concomitant unfavorable medical condition, a witness may sign the consent form in the signature space. It is understood that the witness:
   - must not be part of the study group as defined in the "Register of personnel dedicated to the Clinical Investigation" compiled by the Sponsor during the monitoring visit dedicated to the opening of the Center in agreement with the Investigator responsible for the investigation;
   - it must be impartial, i.e. not the bearer of its own interest in the patient's enrolment in the investigation.

b) If a patient has previously been declared by a court or legal judgment unable to provide for his or her interests, or the patient is legally disqualified and therefore has a legal representative, the consent will be expressed by the legal representative himself who, if he or she accepts the patient's participation in the investigation, must also sign and date the consent form.

c) Given the expected type of patients who can be enrolled in the survey, i.e. elderly patients mostly of very advanced age, as already found in normal clinical practice, there is a high possibility that many of these patients are in fact unable to provide for their own interests but that they have not previously been declared interdicted by a judicial or legal ruling, therefore not equipped with a legal representative. This condition would lead to the exclusion from the investigation of a significant percentage of eligible patients due to the impossibility of collecting informed consent (an inclusion criterion would be missing). In order to safeguard the achievement of an adequate sample size of the study population in a reasonable time, and in order to limit as much as possible the selection of patients (patients of very advanced age are the most representative in proximal femur fractures), if a patient is in fact unable to provide for his or her own interests but is not legally prohibited, The information will be addressed to the patient's family member or cohabitant, who may express consent on behalf of the patient by signing and dating the form in the appropriate signature space.

Note:

- In this condition, the patient's family member or cohabitant is entitled to act pursuant to Art. 105 paragraph 3, Legislative Decree 101/2018 *"When, in the context of processing for scientific research purposes, specific circumstances identified by the rules of ethics are such as to allow one subject to respond in the name and on behalf of another, as a family member or cohabitant, the information may also be provided through the respondent".*

4.3 Obtaining informed consent in emergency conditions

Whenever objectively possible, the consent form will always be signed and dated by the patient or respondent (witness, legal guardian or family member/cohabitant of the patient) prior to verification of inclusion criteria, which is the first procedure under this Protocol.

In emergency situations, i.e. when due to:

- the patient's medical condition and/or;
- the clinical context in which the Investigator and/or will operate;
- of the impossibility of the respondent to be immediately present.

It will not be possible to provide information on the survey and receive any clarifications; the patient or the respondent will be informed as soon as possible about the possibility of participating in this observational survey and will be able to express their consent even later according to the methods described above.

5 Information for the general practitioner

The Sponsor with the documentation relating to this Clinical Investigation will provide the Investigators with a pre-printed information letter to the treating physician containing all relevant information regarding this observational investigation. Once the patient inclusion and exclusion criteria have been verified, if the patient will indeed be included in the investigation, the Investigator will fill in the pre-printed letter with the patient's data and deliver this letter to the patient himself or to the respondent subject who will be in charge of delivering it for information to the general practitioner.

6 Any news regarding the medical device under investigation

In the event that, during the course of this Clinical Investigation, the Investigator or the Sponsor becomes aware of news regarding the Chimaera system, deriving from this investigation or from market reports (*complaints*), which may influence the decision of the patient (or the respondent) to participate in the Clinical Investigation, it will be the Investigator's responsibility to promptly inform each subject already enrolled in the Investigation.

It is understood that, following this new information made available, the patient (or respondent) or the Investigator may refuse to continue the investigation at any time they wish without prejudice to subsequent care.

7 Vulnerable population and treatment in emergency circumstances

Given the observational nature of this Clinical Investigation, this protocol does not provide for any special procedures, i.e. procedures that are different from those already implemented through normal clinical practice for the management of vulnerable populations and emergency circumstances.

8 Preclinical Evidence and Previous Clinical Experience

Orthofix Srl has developed and placed on the European market the Chimaera after carrying out an evaluation of the clinical performance and safety of the medical device on the basis of biomechanical tests and clinical data obtained from scientific publications on equivalent products (on request, more details available in Technical File A.1.10 archived at the Sponsor).

The outcome of this pre-market assessment established that the Chimaera meets the necessary requirements for CE marking, in particular it has an acceptable risk/benefit ratio when used according to the manufacturer's indications for use.

This observational clinical investigation is the first clinical trial carried out on the Chimaera system, so no clinical reports are available from previous clinical trials carried out by the Sponsor.

Sales data show that to date the treatments carried out in Europe with Chimaera are more than 3000: the frequencies of serious complications received by Orthofix Srl through the passive medical device vigilance system are lower than those reported in the literature for equivalent nails on the market for several years. This first evidence seems to confirm the efficacy and safety of the technical characteristics integrated into the device; however it must be integrated with clinical data that will be collected through the present observational investigation.

9 Information related to the clinical investigation

9.1 Description of the clinical investigation

This clinical investigation is part of the active medical device vigilance plan that Orthofix Srl, in agreement with its Certifying Body, has planned to actively collect clinical data relating to the use of Chimaera in a representative number of users and patients. The data obtained from this Clinical Investigation will be used to complement the pre-market clinical evaluation carried out on the Chimaera with post-market clinical data from the use of the device in normal clinical practice (more details reported in the rationale of the Clinical Investigation).

9.2 Design of the Clinical Investigation

The present clinical investigation is of the following type:

- Observational (as ascertained in the feasibility phase, the procedures reported in this Protocol are part of the normal clinical practice of the Centers involved);
- post-market (the medical device observed has a CE mark and is already used in the Sites involved);
- prospective (clinical data will be collected from patients who will be treated with the observed device after signing the informed consent);
- uncontrolled (only the medical device under study will be observed);
- non-randomized (since the Survey is observational and uncontrolled, a randomized assignment of the medical device is not applicable);
- multicenter (the Survey will be conducted in 8 Centers);
- national (the Sites involved are all located in Italy).

Considering the purpose and design described above, this Clinical Investigation falls within the type of studies defined as "*Post Market Clinical Follow-up (PMCF) study*" (more details in MEDDEV 2.12/2 rev. 2).

9.3 Objectives of the Clinical Investigation

The purpose of this Clinical Investigation is to actively collect clinical data related to the use of the *Chimaera* in a representative number of users and elderly patients with proximal femur fracture, observed in the short (1, 3 and 6 months) and medium (1 year) period after the application of the device.

- The primary objective of the Clinical Investigation is to evaluate the safety of the Chimaera which will be measured in terms of serious device-related adverse events.
- The secondary objective of the Clinical Investigation is to evaluate the clinical efficacy of the Chimaera through a specific functional score.

Note:

For more details regarding the measurement of primary and secondary objectives, please refer to the "*Endpoint*" paragraph of this Protocol.

9.4 Endpoint

In the present Clinical Investigation, the two variables chosen as *the primary and secondary endpoints* to measure the primary and secondary objectives of the Survey also coincide with the measures of response to treatment, in particular:

- *Primary endpoint* (security measure):

  the safety of the *Chimaera* will be measured by the percentage of patients who within a 6-month observation period, due to serious adverse events related to *the Chimaera,* will have to undergo a second operation to continue with the treatment of the proximal femur fracture.

- *Secondary endpoint* (efficacy measure):

  the effectiveness of the treatment carried out with *Chimaera* will be measured through the Bowers & Parker functional score for the evaluation of the patient's functional recovery.

  Note:

  Bowers & Parker's functional score[7] It is a validated and unanimously recognized reliable score for the evaluation of patients treated following a hip fracture. This score assesses the patient's functional recovery (in terms of pain, walking ability and social independence) compared to the patient's condition before the fracture. The Bowers & Parker score also has predictive value for assessing the long-term mortality of the treated patient, and for planning short-term rehabilitation activities.

9.5 Variables to measure

The primary endpoint (safety measure) of the present Clinical Investigation will be measured as follows:

- the correlation of the serious adverse event to the *Chimaera* will be freely assigned by the Investigator according to the following options: unrelated/potentially related/certainly related. Serious events potentially or certainly related to the *Chimaera* will be included in the calculation of the security measure.
- It is understood that, for serious events judged to be potentially or certainly related to the *Chimaera*, the Sponsor reserves the right to supplement the Investigator's assessment with an opinion from an independent orthopaedic physician and with a technical analysis of the implanted and removed device to proceed with the second intervention. Following these analyses, if the removed device complies with the design specifications, and if the independent orthopedist finds an operating technique error in the primary implant, in agreement with the Investigator, the event initially classified as potentially or certainly related to the *Chimaera* may be reclassified as unrelated and, therefore, will be excluded from the calculation of the safety measure. Similarly, serious adverse events due to use that does not comply with the manufacturer's instructions for use, otherwise referred to as *off label use*, will be excluded from the calculation of the safety measure.

The *secondary endpoint* (efficacy measure) of the present Clinical Investigation will be measured as follows:

- The Investigator will fill out a scale (Appendix 1) for each patient at each of the follow-up visits (1, 3, 6, and 12 months). If necessary, a translation of the scale into Italian is also provided to support comprehension.
- As suggested by the authors, the scale can be filled in by the Investigator on the basis of the answers provided by the patient, even by telephone. Given the type of patients that will be recruited, mostly non-self-sufficient elderly people who cannot always be moved easily, this procedure will not involve additional risks for the patient and should limit the number of patients that cannot be assessed due to lack of data on the secondary *endpoint*.

Data for the primary and secondary *endpoints* will be:

- reported in the patient's medical record and recorded in the electronic database provided free of charge by the Sponsor to each Investigator to collect the data of the Clinical Investigation;
- they will be analyzed using descriptive and/or quantitative statistics and presented with their respective confidence intervals (more details in the Statistics section of this Protocol).

9.6 Patients selection

An adult patient with a previously untreated proximal femoral fracture who, in the Investigator's sole judgement, has an appropriate indication for surgical treatment with Chimaera will be considered eligible for the Clinical Investigation. Patients who meet all of the following inclusion criteria and none of the exclusion criteria will qualify for enrolment in this Clinical Investigation.

9.6.1 Inclusion criteria

A patient will be considered eligible for participation if:

- directly or indirectly (through a legally acceptable representative), he/she has expressed the willingness to participate in the Investigation by signing and dating the informed consent form;
- he/she is at least 65 years of age at the time of signing the informed consent form;
- he/she has been diagnosed with a stable or unstable fracture in the pertrochanteric, intertrochanteric, or subtrochanteric region of the femur, not previously treated;
- in the opinion of the Investigator, he/she has a standard indication for surgical treatment with an intramedullary nail;
- the fracture will be treated with the short (length = 180 mm) Chimaera nail and one or two telescopic cephalic screws, in accordance with the manufacturer's instructions for use.

9.6.2 Exclusion criteria

A patient will be considered not eligible for participation if:

- he/she is undergoing surgery to address the sequelae of a previously treated fracture;
- he/she has been diagnosed with a pathological fracture of oncologic origin (primary tumour or skeletal metastasis);
- he/she has been diagnosed with a fracture in the diaphyseal and/or distal region of the femur;
- he/she has been diagnosed with an open proximal femoral fracture (type II or III according to the Gustilo and Anderson classification);
- he/she has been diagnosed with multiple fractures (including bilateral proximal femoral fractures);
- during the preoperative or intraoperative phase, it is decided to treat the fracture with the long version of the Chimaera nail and/or with non-telescopic (fixed-length) cephalic screws;
- he/she has a medical condition that constitutes a contraindication to treatment with Chimaera according to the manufacturer's instructions for use;
- he/she has a suspected or confirmed hypersensitivity/allergy to any component of the device that comes into contact with the patient;
- he/she presents with any clinical condition that, in the opinion of the Investigator, could interfere with the Clinical Investigation procedures or compromise patient safety;
- he/she is concomitantly treated with a non-permitted device that cannot be removed without compromising patient safety;
- he/she is participating in another clinical study or has participated in another clinical study within 3 months prior to signing the informed consent form.

9.7 Expected Number of Patients to be Enrolled

Considering the high proportion (approximately 25%) of anticipated premature withdrawals in this patient population, in order to obtain a sample of 300 patients completing the Investigation, a total of 400 patients are planned to be enrolled across 8 sites. Accordingly, each site is expected to enrol approximately 50 patients over a period of 6–8 months (estimate based on the current frequency of Chimaera use as reported by the sites during the feasibility phase).

9.8 Enrolment Timepoint

Each eligible patient able to provide consent personally will be considered enrolled in the Clinical Investigation at the time of signing and dating the informed consent form, in accordance with the procedures for collection described in this Protocol.
It is understood that patients unable to provide consent personally will be considered enrolled in the Clinical Investigation at the time of signature by the legally acceptable representative.

9.9 Expected Number of Medical Devices to be Used

Considering the observational nature of the Investigation and that, according to the selection criteria, only one medical device under observation (Chimaera) may be applied to each patient, in line with the expected number of patients to be enrolled, a total of 400 devices are planned to be used across 8 sites. Accordingly, each site is expected to use approximately 50 devices.

9.10 Duration of the Clinical Investigation

The duration of the Investigation for each patient is 12 months, from the signing of the informed consent form to the last follow-up visit.

Considering that the enrolment period is expected to last 6–8 months, the overall anticipated duration of the active phase of the study is 18–20 months, from the signing of the informed consent form by the first enrolled patient to the last follow-up visit of the last enrolled patient.
It is understood that, following the closure of the active phase of the study, unless otherwise agreed with the Investigators and/or Ethics Committees, the Sponsor reserves a period of 6 months to conduct the end-of-study activities, namely:

- database review;
- opening and resolution of potential data clarification requests (queries) to the Investigators;
- preparation of the statistical report;
- preparation of the clinical report;
- site close-out visits;
- end-of-study notifications to the relevant Ethics Committees and Competent Authority.

9.11 Medical-Surgical Procedures and Follow-up of the Clinical Investigation

After obtaining informed consent, the physician will include in the study those patients who, at the screening visit (Visit 0), meet all selection criteria. During the screening visit, the Investigator will also collect demographic data and the patient's medical history.

Enrolled patients, as would also occur if they chose not to participate in the present Investigation, will undergo the surgical procedure (Visit 1) required for the application of the investigational medical device (Chimaera), which marks the beginning of the treatment period.

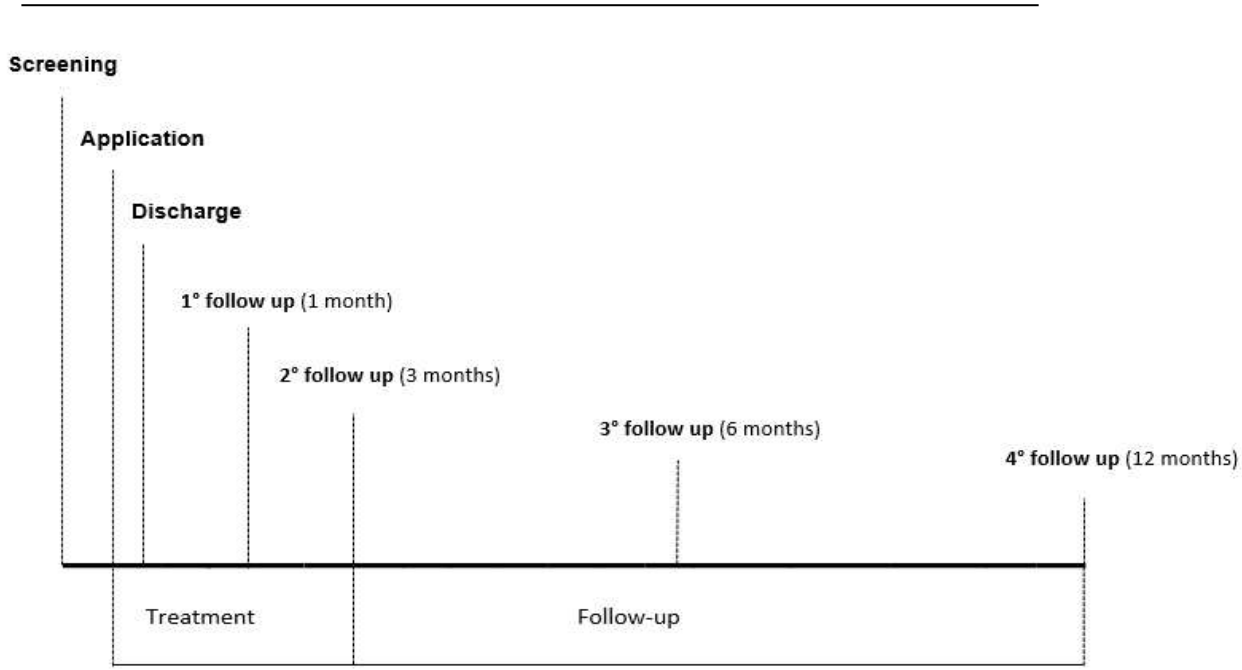
Following the surgery, the patient will attend five subsequent visits. The first three visits after the surgical procedure are part of the treatment period and are:

- the visit performed at hospital discharge (Visit 2), which, unless complications occur, will take place within 10 days after the date of surgery. During this visit, the physician will perform routine assessments to confirm that the operation and postoperative course have proceeded appropriately;
- the following two visits (Visits 3 and 4), were conducted at 1 month and 3 months after the date of surgery, respectively. These visits conclude the treatment period which, in the absence of complications, is expected to be within 8–12 weeks from the date of surgery, with the consolidation of the treated proximal femoral fracture. Healing will be assessed by the Investigator through radiographic evaluation, performing a qualitative assessment of bone density at the fracture site and the alignment of the bone fragments. Starting from Visit 4 and at all subsequent visits, the Investigator will also complete the Bowers & Parker functional score (efficacy measure) to assess the patient's functional recovery.

For these patients, device removal is not planned unless required due to serious adverse events necessitating a second surgical procedure to complete the treatment of the fracture (safety measure). Once the treatment period is concluded, the follow-up period begins, during which two visits will be conducted (Visits 5 and 6), respectively at 6 months and 1 year after the date of surgery. During these visits, clinical data will be collected to monitor the progression of fracture consolidation, the patient's functional recovery, and the occurrence of any medium-term adverse events.
Clinical data from the study will be recorded in the patient's medical chart and entered a validated electronic data capture system provided by Orthofix Srl.
Patients who, for any reason, decide to withdraw their consent to participate in the study before completing the final follow-up visit will continue to receive the same standard of care they would have received had they completed the study.

Note:
The visits and procedures described above are summarized in the patient treatment schedule and in the table of procedures applicable to each visit below.

9.12 Patient treatment schedule



9.13 Table of procedures applicable to each visit

PERIOD		ENROLMENT	TREATMENT				FOLLOW-UP	
VISIT	Number	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Type	Selection	Surgery	Discharge	1° Follow up	2° Follow up	3° Follow up	4° Follow up
	Window	Day 0 ± 1 week	Day 0	Day 5 ± 5 days	Month 1 ± 1 week	Month 3 ± 1 week	Month 6 ± 1 week	Month 12 ± 1 Month
Informed Consent		x						
Verification of Selection Criteria		x	x	x	x	x	x	x
Demographics		x						
Medical History		x						
Radiographic Examination		x	x			x		
Device Implantation			x					
Parker score						x	x	x
Safety Measures			x	x	x	x	x	x

9.14 Predictable factors that can compromise results

The procedures described in this Protocol are part of the normal clinical practice of the Centers involved. In fact, this clinical investigation is observational so it will not change the clinical protocols currently in use in the Centers involved, nor does it involve additional risks for patients and investigators.

In the present clinical investigation, given the type of patients who will be enrolled, two factors are known that could compromise the outcomes and the interpretation of the results, namely:

- For some very elderly patients who have difficulty moving and with impaired cognitive ability, for example due to senile dementia or advanced neurodegenerative diseases, the assessment of functional recovery may be more difficult.

  The Bowers & Parker Functional Score[7] chosen to assess the patient's functional recovery in terms of pain, walking ability and social independence, as described by the authors, precisely because it could be used in high probability on patients unable to answer reliably, it is composed of questions that can also be answered by the patient's companion (e.g. cohabitant, family member, caregiver, social health worker, etc.), understood as a person who lives in close contact with the patient. The companion can also answer by phone and, given the difficulty of moving this type of patient, this possibility will be very useful to limit the loss of data on the patient's functional recovery in the follow-up period.

- The mortality rate of enrolled patients is about 10% at 10 days after surgery and can reach up to 36% at 1 year. Therefore, a high percentage (25% on average) of non-assessable patients, i.e. discontinued before the end of the treatment period for supposed recovery (scheduled for the check-up visit in the third month after the operation), is expected in the present clinical investigation.

  In order to increase the probability of reaching the expected sample size, i.e. 300 evaluable patients, i.e. who will complete at least the scheduled follow-up visit at the third month after the operation (Visit 4), the Sponsor has planned the enrollment of 400 patients and has agreed with the Investigators on a patient replacement procedure described below.

9.15 Interruption and withdrawal of subjects from clinical investigation

A patient will be discontinued prematurely from the study if they do not complete the last protocol-scheduled follow-up visit due to any of the following causes:

- the patient withdraws consent to participate in the study;
- one of the inclusion criteria will be dropped or an exclusion criterion will occur;
- lack of response to treatment that generates an unacceptable risk for the patient and prevents the continuation of the treatment covered by this observational scientific research;
- onset of a serious adverse event that generates an unacceptable risk for the patient and prevents the continuation of treatment;
- the patient does not follow the procedures of the clinical protocol provided by his doctor;
- decision of the Investigator in the interest of the patient;
- patient no longer available (lost to follow-up);
- death of the patient during the study period.

Patients who are prematurely discontinued will be reported in the data collection form through the appropriate discontinuation visit. The Investigator will have the obligation to report to the Sponsor the patients who are prematurely discontinued and, if the patient is not assessable, or is discontinued before the end of the treatment period for supposed recovery scheduled for the control visit at the third month after the operation), may agree with the Sponsor on the replacement of the patient according to the following procedure.

9.16 Patient replacement

Upon notification to the Sponsor, no later than the study recruitment period, non-evaluable patients, at the discretion of the Investigator, may be replaced with a patient who will be assigned a new and unique identification code.

Considering the high percentage of withdrawal usually found with this type of patient, this procedure has the sole purpose of increasing the probability of reaching the expected sample size in terms of evaluable patients. It is understood that the Sponsor will also collect, store and analyze data from prematurely discontinued and replaced patients.

10 Clinical investigation monitoring plan

In order to ensure the proper conduct of the study and the correct recording of study data, at least the following monitoring visits will be planned:

- study start visit;
- two monitoring visits during the active conduct phase of the study;
- Closing visit of the study.

It is understood that, if necessary, for example if numerous deviations from this Protocol occur on a Site,

the Sponsor reserves the right to carry out additional monitoring visits during the live phase of the study.

Prior to each visit, the monitor will contact the Investigator to check availability and schedule the date of the visit, after which they will send a written confirmation specifying the purpose of the visit and any documents to be made available.

On each visit, the monitor must:

- check the updating of the study documentation;
- verify that the Clinical Investigation is conducted and that the data are produced, recorded and communicated in accordance with this Protocol, the Code of Good Clinical Practice – GCP and the applicable legislation;
- verify the correctness of the data entered in the data collection form towards the source data;
- implement any corrective actions.

Note:

The Sponsor intends to monitor the totality of data reported in the informed consent forms, inclusion and exclusion criteria, variables related to study endpoints, and all information regarding serious or non-serious adverse events. If deemed appropriate and necessary, the other data from the study may also be monitored.

11 Clinical Investigation Documentation

During the study initiation visit, the monitor will provide the Investigator responsible for the clinical investigation with a file containing all the paper documentation necessary for the management of the study, namely:

- study protocol with related Synopsis and appendices;
- copy of the approval of the Ethics Committee of reference;
- an original copy of the signed and approved economic agreement;
- list of participating centers;
- information regarding the medical device under observation (Instructions for use and surgical technique);
- certification relating to the CE marking of the device;
- patient information sheet and consent collection form;
- information letter for the attending physician;
- Adverse event reporting form;
- a copy of the data collection form;
- the eCRF access credentials and the platform user manuals.

Note:

The monitor will also deliver an electronic copy, non-modifiable, of all the study documentation for consultation and possible printing according to the needs of the Investigator.

As required by Good Clinical Practice guidelines:

- in order to prevent accidental or premature destruction of study documents, it will be the responsibility of the Investigator to keep the file in a secure environment with controlled access;
- for the entire duration of the clinical investigation, the study documentation must be updated and made available during the monitoring visits;
- the documentation relating to the study should be kept for the longest possible duration and, at least, for 7 years after the completion or conclusion of the Survey.

In the event that the Investigator relies on a third party for the preservation of the documents, he shall inform the Sponsor of the place of storage and the procedure for transferring the file.

12 Data management

No later than the study start visit, the Sponsor will provide an electronic data collection system (eCRF), called Symphony, free of charge, on which all data from this Clinical Investigation will be collected.

Symphony is an EDC (*Electronic Data Capture*) solution developed and validated by Arithmos Srl, which is an ISO 9001 and ISO 27001 certified company. *Symphony* therefore has an Information Security Management System in line with international regulatory standards and ensures compliance with regulations by monitoring and archiving the *audit history* directly on the platform.

For more details contact:

ARITHMOS Srl

Via Roveggia 122 – 37136 Verona ITALY

Tel.: +39 045 58549

Fax: +39 045 8209471

info@arithmostech.com

No later than the study initiation visit, the Sponsor will provide the Investigators with the necessary training for the correct use of *Symphony.* Furthermore, if necessary, for the entire duration of the Investigation, the Sponsor will maintain a free *help desk* service to support the Investigator.

Each Investigator will be able to access *Symphony* via the internet with private credentials and will only have visibility of the data relating to the patients recruited in their Center. The Investigator assumes responsibility for ensuring that data is entered into the eCRF in a timely manner, i.e., within 2 calendar weeks of the date of the visit.

The processing of clinical data collected through this Clinical Survey will be processed anonymously by the Sponsor in compliance with European data protection legislation, i.e. the General Data Protection Regulation no. 2016/679 (*General Data Protection Regulation* or GDPR).

13 Quality Assurance

In order to ensure the correct conduct of the Clinical Investigation in accordance with *Good Clinical Practice*, the UNI EN ISO 14155:2012 Standard and in accordance with the provisions of this Protocol, the Sponsor:

- during the live phase of the Investigation, it provided for a monitoring plan (described above);
- moreover, if necessary, both during and after the live phase of the Investigation, the Quality Assurance department of the Promoter (as well as national or international regulatory authorities) may perform an audit at the Sites with at least 15 days' notice.

14 Deviations from the clinical evaluation plan

All deviations from this Protocol, detected by the monitor during visits to the Center or spontaneously reported by the Investigator, will be recorded by the Sponsor and stored among the data related to the study.

Each deviation, both borne by the Investigator and the *non-compliant* patient, will be analyzed by the Sponsor and classified as a major or minor deviation. Following this assessment, the Promoter will put in place the corrective actions envisaged by GCP to prevent the deviation from happening again and, if necessary, promptly inform all Investigators and their Ethics Committees.

In addition, at the end of the clinical investigation, the list of deviations will be analyzed to verify any impairment in the interpretation of the results affected by the deviations.

15 Amendments to the clinical evaluation plan

In the event that amendments to this Protocol are necessary, the Promoter:

- classify the nature of the amendments as substantive or non-substantive;
- modify the Protocol and the study documentation affected by the amendments by keeping track of the changes made;
- in the case of non-substantial amendments, for information, it will promptly notify the participating Sites and the related Ethics Committees in writing by sending a copy of the amended documents;
- in the case of substantial amendments, it will suspend the clinical investigation until a new favourable opinion is issued by the Ethics committees involved.

16 Early termination and suspension of clinical evaluation

Early termination occurs when a clinical trial is definitively stopped earlier than planned, i.e., before the end-of-study visit for each Center. The suspension is intended as a temporary interruption which, only following corrective actions and a new assessment and approval by the Ethics Committees involved, can be resumed.

Both the Sponsor and the Investigator reserve the right to interrupt or suspend the Investigation at any time for serious and documented reasons, such as, but not limited to:

- following the emergence of new scientific evidence, or following an interim analysis, or following notifications of *complaints* or the occurrence of an unexpected serious adverse reaction, the continuation of the Investigation constitutes an unacceptable risk for patients;
- clear lack of treatment effect in a significant number of patients due to causes directly attributable to the medical device observed;
- difficulty in enrolling a sufficient number of participants in a reasonable time;
- excessive number of patients withdrawn prematurely and not assessable.

It is understood that:

- any suspension or early termination of the Investigation will be promptly communicated to all enrolled patients including those who have completed the study, to all Investigators and their Ethics Committees, as well as to the competent authority with which the Investigation will be registered;
- upon the occurrence of the early termination of the Investigation, the Promoter will pay the fees accrued up to that moment to the entity with which it has entered into the economic agreement.

17 Adverse events

Foreseeable adverse events from the use of *Chimaera,* as identified by the risk analysis carried out on the product at the design stage, are described in the "POSSIBLE SIDE EFFECTS" section of the package insert of the device (http://abs.orthofix.it/db/resources/PQ_HFN.pdf) in the section.

This clinical investigation is observational and therefore does not involve additional risks for patients and investigators.

Definitions:

- An AE is any unwanted experience associated with the use of the device in a patient.
- An AE is described as a serious AE when the patient, due to that AE:
    - dies;
    - suffers a potentially fatal event;
    - undergoes a prolongation of hospitalization;
    - he undergoes a second hospitalization;
    - reports a permanent disability
    - Reports a birth defect.

Adverse events and effects that will occur during the study will be classified and reported to the Sponsor through the appropriate form provided with the study documentation. The Investigator will be obliged to notify the Sponsor of a serious adverse event within 24 hours of becoming aware of it.

In compliance with the reference legislation (art. 9 of Legislative Decree 46/97 and MEDDEV 2.12.1) moreover, through the use of the ministerial forms, the Investigator and the Sponsor will report to the Ministry of Health all accidents that will occur during the use of the medical device subject to this study by means of a specific report to office V of the DGDMF, as well as to the local EC.

18 Statistics

For this clinical investigation, there are no statistical hypotheses to be tested or direct comparisons with other devices clinically equivalent to the *Chimaera*, so no threshold has been defined to be considered safe and effective.

However, for the sole purpose of recruiting enough patients to be able to consider the data collected for the *primary endpoint* (safety measure of response to treatment) reliable compared to the data reported in the literature, a sample sizing calculation was still performed.

For Chimaera-equivalent devices, the proportion of patients who underwent a second surgery (due to serious device-related adverse events and/or due to device failure) in the literature is reported to be between 3% and 10% depending on the study considered. A sample size calculation was then performed in order to limit the upper limit of the 95% confidence interval of the proportion of patients with second surgery to below 10%.

The following table shows the number of patients and the upper limit of the confidence interval for different possible values of the percentage of the primary *endpoint* (calculations were made using the statistical method of the exact binomial):

Percentage of patients with second intervention	Upper limit of the 95% confidence interval	Number of patients observed
3%	8.518%	100
4%	9.926%	100
5%	9.614%	160
6%	9.703%	250
7%	9.958%	400

Based on the frequencies of serious device-related adverse events and/or device failures received by Orthofix Srl through the passive medical device vigilance system since the device was placed on the market, the expected percentage for the primary *endpoint* is no more than 6%. Therefore, the expected enrollment of 400 patients that will potentially allow us to obtain a sample of 300 evaluable patients is considered adequate for the type and objectives of the present clinical investigation.

The clinical data collected during this Clinical Survey will be analyzed through descriptive statistics:

- the *primary endpoint* will be presented as a percentage value and the corresponding 95% confidence interval;
- the *secondary endpoint* (Bowers & Parker functional score) and other radiographic parameters will be presented via quantitative descriptive statistics (mean, standard deviation, median, minimum, maximum, 95% confidence interval).

During the present Clinical Investigation, if necessary, an interim statistical analysis of the collected data could be carried out, e.g. when all patients have completed the third post-operative check-up (expected within 6 months from the date of operation).

The clinical data obtained from this Clinical Investigation will be used to complete the evaluation of the clinical performance and safety of the *Chimaera* in order to confirm that the device can be considered

effective and safe as assumed under development based on pre-clinical evaluations carried out for obtaining the CE mark.

19 Dissemination of results

The Investigators and the Sponsor undertake to keep the clinical data collected through this Clinical Investigation confidential and confidential until the information is made public in anonymized form by the Sponsor at the end of the Investigation.

Within six months of the last visit to the closure of the Site, the Sponsor assumes responsibility for making the data of the Survey public through the preparation of the final clinical report, containing the aggregated and analysed data of all the Sites, which will be sent to all the Investigators, the Ethics Committees involved and the Competent Authority.

In addition, within 6 months of the finalization of the final clinical report, the Sponsor reserves the right to publish a manuscript containing the aggregated and anonymized data of the multicenter.

At the end of the Survey, the Sponsor will make the results of the patients enrolled in the Site available for publication to each Site.

The Sponsor reserves the right to present the results of this study at scientific meetings or to present these data also to national and international authorities. Furthermore, the Sponsor recognizes the right and interest of all participating Investigators to scientifically publish or disseminate at congresses and meetings the results obtained from this Clinical Investigation.

20 Data Publication Policy

The Sponsor undertakes to share with all Investigators for knowledge and review any preliminary version of the multicenter manuscript before publication.

Any publication by the Investigator may only take place after any multicentre publication by the Sponsor. It is understood that:

- the Investigator may initiate a publication prior to any multicenter publication made by the Sponsor only with the written consent of the Sponsor;
- where no publication has been initiated by the Sponsor within six months of the finalization of the final clinical report, the Investigator will be free to publish the results obtained in his/her Center without the written consent of the Sponsor.

Prior to any publication or presentation of the results, the Investigators undertake to send in due time (in any case not less than 30 days prior to publication or submission) the manuscript/abstract/presentation to the Sponsor for review and approval. The Promoter undertakes to return a revision within 15 days from the date of receipt of the draft.

It is understood that the Promoter's review is aimed at ensuring the correct reprocessing and presentation of the results of the Survey. Changes proposed by the Promoter shall not in any way interfere with the scientific nature and content of the publication.

The identity of the Sponsor and the nature of its contribution to this Clinical Investigation shall be made explicit in any publication or presentation at congresses or meetings with the utmost respect for the transparency of data in clinical research.

21 Paternity (authorship)

In compliance with the "Uniformity requirements for submitting Manuscripts to Biomedical Journals" of the International *Committee of Medical Journal Editors (ICMJE)*[8], all those who meet the following conditions will be considered authors of the manuscript:

a) They have contributed substantially to the conception or design or acquisition or analysis and interpretation of data;

b) They have contributed substantially to the drafting of the article or to its critical revision for the important intellectual contents;

They gave final approval of the version to be published.

All other participants who contributed to the study (whether by enrolling patients, or in other ways) will be mentioned in the section *"Acknowledgments"* of the manuscript. For any other eventuality, the indications provided by the ICMJE will be followed and respected.[8]

22 Bibliography

1. Close JD, Swartz K, Deu R. Hip fracture in older patients: tips and tools to speed recovery. *The Journal of family practice.* 2013; 62(9):484-492.
2. Sheehan SE, Shyu JY, Weaver MJ, Sodickson AD, Khurana B. Proximal Femoral Fractures: What the Orthopedic Surgeon Wants to Know. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2015; 35(5):1563-1584.
3. Innocenti M, Civinini R, Carulli C, Matassi F. Proximal femural fractures: epidemiology. *Clinical cases in mineral and bone metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases.* 2009; 6(2):117-119.
4. Orive M, Aguirre U, Garcia-Gutierrez S, et al. Changes in health-related quality of life and activities of daily living after hip fracture because of a fall in elderly patients: a prospective cohort study. *International journal of clinical practice.* 2015; 69(4):491-500.
5. Sciard D, Cattano D, Hussain M, Rosenstein A. Perioperative management of proximal hip fractures in the elderly: the surgeon and the anesthesiologist. *Minerva anesthesiology.* 2011; 77(7):715-722.
6. Prestmo A, Hagen G, Sletvold O, et al. Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial. *Lancet (London, England).* 2015; 385(9978):1623-1633.
7. Bowers TM, Parker MJ. Assessment of outcome after hip fracture: development of a universal assessment system for hip fractures. *Sicot-j.* 2016;2:27.
8. ICJME. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals. 2018; http://www.icmje.org/recommendations/. Accessed 05 March, 2019.

Appendix 1: Bowers & Park Scale

Mobility (select the appropriate condition using the left column) A score of one represents a patient who has no need for any walking aid and has no restriction in walking distance, through to 10, which represents a bedbound individual.		
	1	Never uses any walking aid and no restriction in walking distance.
	2	Never uses any walking aid, but walking distance limited to less than one kilometre.
	3	Occasionally uses a walking aid when out walking.
	4	Normally uses one walking stick or needs to hold on to furniture.
	5	Normally uses two sticks or crutches.
	6	Mobilises with a frame alone, without the need for assistance.
	7	Mobilises with a frame and the assistance of one other person.
	8	Mobilises with a frame and the assistance of two people.
	9	Bed to chair (with or without assistance), or wheelchairbound.
	10	Bedbound most or all of the day.

Social dependence (select the appropriate condition using the left column) Give a value of one for a person who is completely independent and living at home not requiring any support or assistance, to eight which is a fully dependant requiring patient requiring care in hospital		
	1	Completely independent. Requires no assistance in basic or advanced activities of daily living (ADL) including shopping.
	2	Minimal assistance. Requires occasional help up to twice a week from family, friends or other services with some activities such as shopping or gardening.
	3	Moderate assistance. Requires regular assistance more than twice a week but less than seven times a week with some ADL such as bathing, washing or heavy housework.
	4	Regular assistance. Requires daily help to assist with ADL.
	5	Dependent. Requires regular help more than once a day with many basic ADL such as preparing food and housework but remains living at home.
	6	Severely dependent. Living in residential care. Full-time care facility but independent of at least one basic ADL such as being able to dress or go to the toilet without help.
	7	Fully dependent. Living in nursing home, skilled nursing home or long-term hospital facility with full-time nursing care. Patient requires assistance in most ADL living such as washing, dressing and getting to the toilet.

	8	Patient temporarily resident in hospital requiring both nursing and medical care.

Pain (select the appropriate condition using the left column) A score of zero is given if the patient or their attendant carer is unable to answer, else the pain is rated one (no pain in the hip) to eight (constant and severe pain requiring regular strong analgesia).		
	0	Unable to answer.
	1	No pain at all in the hip.
	2	Occasional and slight pain. May occasionally take mild analgesia such as paracetamol.
	3	Some pain when starting to walk, no rest pain. Occasional analgesia taken.
	4	None or minimal pain at rest, some pain with activities, frequent mild analgesia.
	5	Regular pain with activities which limits walking distance. Occasional or mild rest pain.
	6	Frequent rest pain and pain at night. Pain on walking. Regular mild analgesia and occasional stronger analgesia taken.
	7	Constant pain present around the hip. Regular mild analgesia and frequent strong analgesia.
	8	Constant and severe pain in the hip requiring regular strong analgesia such as opiates.