Post-Market Clinical Follow-up Observational Study Protocol

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Study code: OCI_2201

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

ClinicalTrials.gov ID: NCT05612139

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INVESTIGATOR SIGNATURE PAGE

By my signature below, I acknowledge that I have read this protocol and I agree that it contains all necessary details for carrying out the study described therein. Furthermore, I agree to conduct this study in compliance with said study protocol, the ICH Good Clinical Practice guideline and ISO 14155, as well as with any applicable national or local laws and regulations and with my contractual obligations towards *Orthofix S.r.l*. or its representatives.

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3. LIST OF ABBREVIATIONS

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

4. SYNOPSIS

TITLE	A single center post-market clinical follow-up (PMCF) observational study evaluating the clinical performance and the safety profile of the JuniOrtho™ Telescopic Intramedullary Nail (JTIN) for the treatment of pediatric patients suffering from Osteogenesis Imperfecta
ACRONYM	JTIN
RATIONALE	This study has been planned as part of the Orthofix Srl post-market active surveillance plan for the collection of data on both the clinical performance and the safety profile of the JTIN. The rationale of the proposed study is to update and support the pre-market clinical evaluation of the JTIN with Real World Evidence clinical data in a real-life surgical setting, in order to confirm the benefit/risk ratio of this medical device and to keep the CE mark under Medical Device Regulation (MDR) requirements.
INVESTIGATIONAL DEVICE	JuniOrtho Telescopic Intramedullary Nail™ (JTIN). The JTIN is a self-extending intramedullary nail (telescopic rod) designed to address the specific demands of osteosynthesis in pediatric patients suffering from osteogenesis imperfect (OI). It is intended for the fixation of femoral and/or tibial fractures, osteotomies, malunions and non-unions. The design of the JTIN includes a female and a male component, which are anchored to the proximal cortex and distal epiphysis through screw-type fixation in femurs, and fixation in proximal and distal epiphysis in tibias. These two components slide from each other, allowing for extension of the JTIN as the bone structures remodel and patient growth occurs.
PROCEDURES	One selected site, experienced in the treatment of pediatric patients with OI, where the usage of JTIN is already part of the normal clinical practice, will participate in this study. Investigator will screen patients treated (or planned to be treated) with JTIN to verify inclusion and exclusion criteria, to achieve the enrollment of 25 cases. With lost to follow-up percentage estimated at 20%, this will lead to a total of 20 evaluable cases, i.e. 20 implanted JTIN (some patients may contribute for more than one implant). Patients are prospectively and retrospectively enrolled in the study: they may have undergone JTIN implantation from the 1st of January 2022. Enrolled patients, since this study is non-interventional and observational, will follow the standard medical practice of the site: no requirements regarding the treatment of patients will be imposed on the site or Principal Investigator and the Sponsor will not in any manner influence the treatment decisions. Data of enrolled subjects will be collected for this study up to 1 year from surgery. The hospital standard care usually, but not exclusively, includes: surgery, discharge and plaster removal visits, and then 3 other follow up visits up to 1 year from surgery (see “Visits and Assessments Schedule”). Visits frequency is estimated as average of the site normal clinical practice, actual visit timing for each patient will be performed according to investigators and hospital staff evaluation. The patient data will be systematically collected by the investigator in eCRF.
PLANNED INVESTIGATION PERIOD	**Preparation:** 4 months for ethics committee submission preparation and approval.

<table>
<tr><td></td><td>Enrolment period:
6 months from site initiation.

Live phase:
Total of 1,5 year (18 months), i.e. 6 months of enrollment period plus 1 year of clinical data collection until the last patient completed follow-up.

Final phase:
6 months including final monitoring, database closure and Statistical and Clinical Study Report writing.</td></tr>
<tr><td>OBJECTIVES</td><td>Primary objective: to evaluate the safety of the JTIN, in terms of percentage of procedures with at least one serious/not serious adverse event certainly or possibly related to JTIN up to 1 year follow-up.

Secondary objectives: to evaluate clinical safety and performance of the JTIN, in terms of: implant survival for safety, bone union achievement and fracture-free survival for performance.

Exploratory objective: The Gillette Functional Assessment Questionnaire will be collected at different times to evaluate the changes after treatment.</td></tr>
<tr><td>TYPE OF THE INVESTIGATION</td><td>This study on JTIN device is a post-market, prospective and retrospective, observational, single-center study, namely a PMCF study. The design will contain a single arm, will be open label and will not involve randomization nor any additional procedure compared to routine practice.</td></tr>
<tr><td>PLANNED INVESTIGATION PERIOD</td><td><table><tr><td>First patient First visit</td><td>Q3 2023</td><td>Last patient First visit</td><td>Q3 2023</td><td>Last patient Last visit</td><td>Q4 2024</td></tr></table></td></tr>
<tr><td>STUDY DURATION PER SUBJECT</td><td>The Study initiation for the subject is to be intended after patient's information and non-opposition (that can be also after the JTIN application surgery). The subject will be treated by the means of JTIN application and will follow standard clinical care of the selected site. If the information and non-opposition occur after the JTIN surgery, previous data will be collected retrospectively. The data from the standard care will be collected for this study up to 1 year follow-up visit.</td></tr>
<tr><td>CENTER(S) / COUNTRY(IES)</td><td><table><tr><th>Hospital</th><th>Country (EU)</th><th>City</th><th>Principal Investigator</th></tr><tr><td>1</td><td>France</td><td>Paris</td><td>Dr. Zagorka Pejin</td></tr></table></td></tr>
<tr><td>PATIENTS / GROUPS</td><td>Clinical data will be collected only on patients with a regular indication for JTIN as per IFU (no off-label use will be included). The JTIN is indicated for fractures, osteotomies, malunions and non-unions in femur and tibia in pediatric patients suffering from osteogenesis imperfecta. The JTIN is intended to be used in pediatric patients, older than 18 months.</td></tr>
<tr><td>INCLUSION CRITERIA</td><td>A patient will be included in the study if:
is in pediatric age ((> 18 month and < 18 years) at the time of surgery;
is skeletally immature;
has a diagnosis for OI;</td></tr>
</table>

	• has a regular indication for surgical intervention with JTIN to treat femoral and/or tibial fractures, osteotomies, malunions and non-unions; • Patient and/or legal representative/guardian is duly informed and doesn't oppose to participation.
EXCLUSION CRITERIA	A patient will not be included in the study who: • has a medical condition that is a contraindication according to the manufacturer's instruction for use; • has any conditions that in the Investigator's opinion may interfere with the study execution or due to which the patient should not participate for safety reasons; • requires the application of, or has already in-situ concomitant devices that cannot be safely removed (except for permitted concomitant devices); • is participating in other clinical trial or has taken part in any clinical study in the last 3 months with exception of analytical trials on genetics study related to OI (i.e. studies that do not include an investigational treatment for the patient such as new drugs or other medical devices); • is likely to be lost to follow up, according to investigator's opinion.
CONCOMITANT MEDICATION/CON-COMITANT DEVICE	K-wires, bone graft and any other concomitant devices, e.g. 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 treatment. It is understood that any necessary medical devices applied on any other bones other than the one treated by JTIN are permitted as well.
SAFETY ENDPOINTS	**Safety endpoints:** The safety profile of JTIN will be assessed by the following safety endpoints: • Percentage (%) of procedures with at least one serious/not serious adverse event certainly or possibly related to JTIN up to 1 year follow-up (primary); • Implant survival rate: it is the percentage of not exchanged nails up to 1 year follow-up.
EFFICACY ENDPOINTS	**Efficacy endpoints:** the clinical performance of the JTIN will be assessed by the means of the: • Bone union achieved; • Post-treatment fracture-free survival up to 1 year follow-up;
EXPLORATORY ENDPOINT	Gillette Functional Assessment Questionnaire will be collected before the surgery and then at bone consolidation assessment and at 1 year follow-up.

CLINICAL PARAMETERS	• Age at surgery
	• Gender, height, weight
	• OI classification
	• Co-morbidities (other acquired or congenital deformities) and family diseases history
	• Concomitant Medication, if applicable
	• Treated Bone/s (femur / tibia)
	• Surgery details (operation time, fluoroscopy time, device variant, other devices, complications—including blood loss)
	• Intraoperative measures (for corrections):
	  ○ Number of osteotomies
	  ○ Rotational correction
	  ○ Varus / valgus correction
	  ○ Shortening

	• Postoperative radiographic measures to assess any deviations from intraoperative measures • ROM and WBP • Bone union assessment • Safety events (AE and MDD)
STATISTICAL METHODOLOGY FOR SAMPLE SIZE CALCULATION	A revision of the literature on the complication rates has been made. The scientific literature reports that the percentage of procedures which develop at least one serious/not serious adverse event certainly or possibly related to the procedure itself is between 9% and 60%, with a mean of 31%. Assuming a complication rate aligned or better than the mean observed in literature (31%), but also considering alignment with literature's results in terms of success rate (bone union), a sample size of 20 procedures will be sufficient to estimate the adverse event rate with 95% confidence interval of the upper limit fund in literature. Considering a drop-out or a non-evaluable rate of 20% of the procedures, a total of 25 procedures should be collected for this study.

4.1 Visits and Assessments Schedule

PERIODS		ENROLMENT	TREATMENT			FOLLOW-UP		
VISITS	Number	*0*	*1*	*2*	*3*	*4*	*5*	*6*
	Description	*Screening*	*Surgery*	*Hospital Discharge*	*Plaster or Immobilizer Removal*	*Bone consolidation assessment*	*2nd Follow-up*	*3rd Follow-up*
	Time Window	*N/A*	*Day 0*	*1 week (± 2 days)*	*2 months (± 2 weeks)*	*5 months (± 2 months)*	*9 months (± 1 month)*	*1 year (± 1 month)*
Information and non-opposition		X						
Inclusion / Exclusion Criteria		X						
Medical History		X						
Concomitant medication		X		X	X	X	X	X
Demographics		X						
X-ray/Fluoroscopy image		X	X		X	X		X
Clinical Examination		X			X	X	X	X
Gillette Functional Assessment Questionnaire		X						X
Device application			X					
Range of motion		X				X	X	X
Weight bearing protocol		X			X	X	X	X
Safety Events			X	X	X	X	X	X
MDDs			X	X	X	X	X	X

Note: timelines and event frequency are estimated as average of the site normal clinical practice, actual visit/event timing for each patient will be performed according to investigators and hospital staff evaluation.

4.2 Schematic Diagram

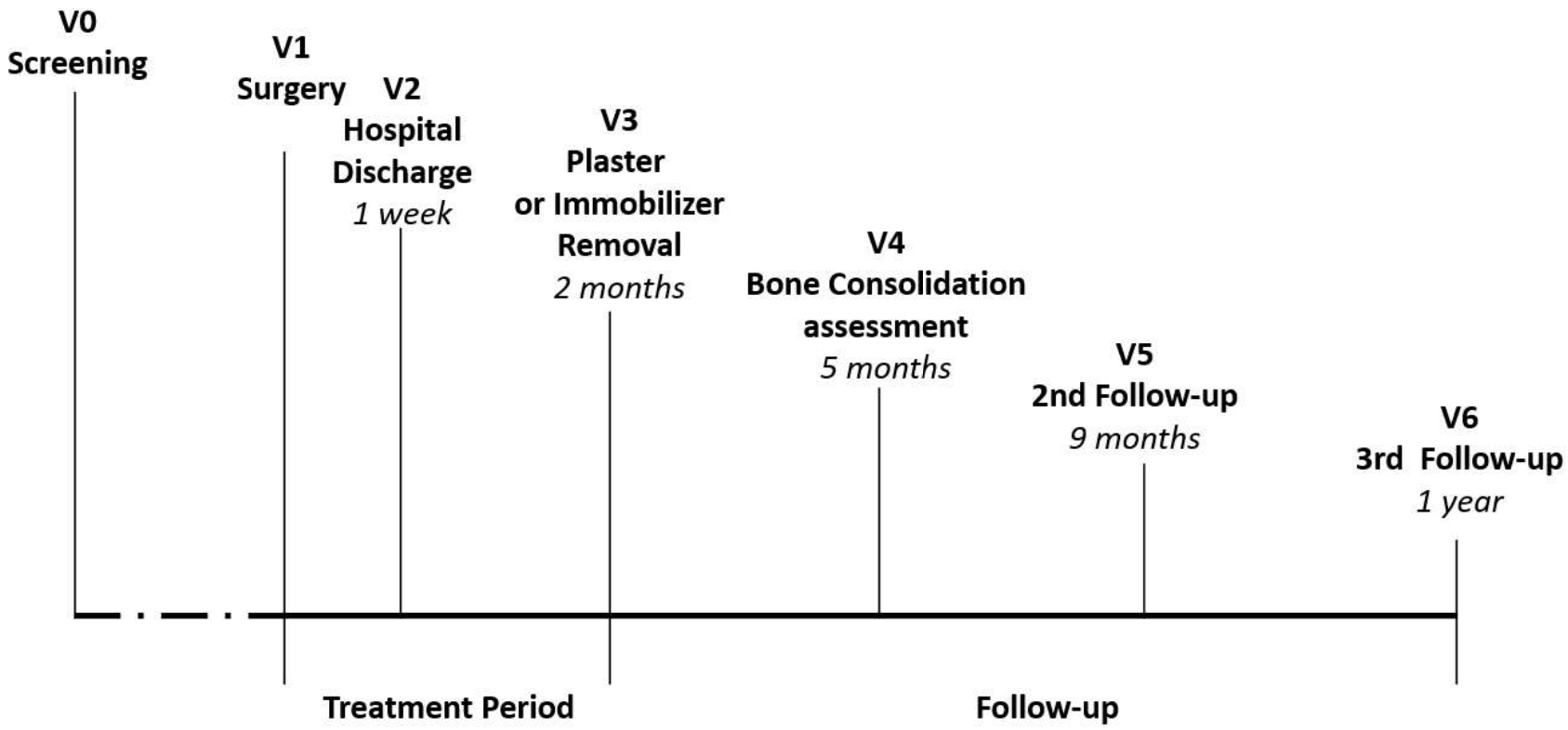

Figure 4:1 Study schematic diagram

Note: timelines and event frequency are estimated as average of the site normal clinical practice, actual visit/event timing for each patient will be performed according to investigators and hospital staff evaluation.

5. INTRODUCTION

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

This document is a PMCF study protocol for a human research study to be conducted according to the last update of: international standard ISO 14155, the European Community guideline on Good Clinical Practice (CPMP/ICH/135/95, ICH-E6, ICH-E11), MDR 2017/745, GDPR- 679/2016, declaration of Helsinki, local applicable regulations and any further update.

5.1 Background Information

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

The objectives of long bone rodding in OI patients are to:
- Fracture treatment;
- Correct deformity;

- Improve function;
- Restore bone density through functional load bearing.

5.2 Rationale of the study

Orthofix Srl put the JTIN on the European market (2021) by the mean of a pre-market clinical evaluation made under the Medical Device Directive (MDD) requirements that was based on the analysis of the scientific literature of equivalent devices.
This study has been planned as part of the Orthofix Srl post-market active surveillance plan for the collection of data on both the clinical performance and the safety profile of the JTIN in a representative population of patients and users.

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

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

The post-marketing, prospective study with CE-marked device JuniOrtho™ Telescopic Intramedullary Nail (JTIN) is designed for gathering real-world medical data from treatment of fractures, osteotomies/ bone deformities, malunions and non-unions in femur and tibia in pediatric patients (older than 18 months) suffering from osteogenesis imperfecta.
All data will be gathered from standard medical documentation from patients who have already been successfully treated with JTIN. Additionally, all procedures that patients underwent are justified by standard of care.
Constant identification of serious or unexpected serious risk related to the use of the device, especially in real-world experience may bring additional data, that can contribute to the safety of future patients.
In conclusion, patients will not directly benefit from the participation in this study but no additional risk related to the study participation is to be recognized.

6. STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of the study is to evaluate the clinical safety profile of JTIN within the scope of its intended purpose, when used according to the manufacturer IFU on a representative population of subjects and users.
To fulfill this objective, one safety endpoint will be evaluated:

- Percentage (%) of procedures with at least one serious/not serious adverse event certainly or possibly related to JTIN up to 1 year follow-up.

The primary endpoint is used to calculate the sample size of the study.

6.2 Secondary Objectives

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

- Implant survival rate: percentage of not exchanged nails up to 1 year follow-up (safety);
- Bone union achievement (performance);
- Post-treatment fracture-free survival up to 1 year follow-up (performance)

These variables will be visually compared with data available on other devices on the market (state-of-the-art).
The sample size was calculated also to provide a significant sample for the evaluation of the following main performance endpoint: bone union achievement.

6.3 Exploratory Objectives

The Gillette Functional Assessment Questionnaire will be collected, according to hospital standard care, before the surgery Visit 0 (screening) and then at bone consolidation assessment (Visit 4) and at 1 year follow up (Visit 6), to evaluate the changes after treatment. The questionnaire is performed by the investigator the first time (i.e. before the surgery) observing the patient (in presence or eventually via telemedicine), and for the follow-up it can be performed by the investigator by telephone or by email with the parent (or legal representative).
The Gillette Functional Assessment Questionnaire is not specific developed for OI patients but it is used in the hospital because no other score is currently available specifically for OI patients. The hospital is aware that other factors for OI patient can interfere with the score.

7. STUDY DESIGN

7.1 Research Type

This is a Post Market Clinical Follow-up (PMCF) study which is prospective and retrospective, observational, single-center, not controlled.
No requirements regarding the treatment of patients will be imposed on the Site or Principal Investigator and the Sponsor will not in any manner influence the treatment decisions of Principal Investigator (i.e. non-interventional). The enrollment of patients and their treatment, including diagnostics and monitoring, will be guided solely by the principles of normal medical practice and the Principal Investigator's sole medical judgment. Site and Principal Investigator will ensure that the Device is used in accordance with normal medical practice and the instructions for use. The subjects will not undergo additional visit nor non-invasive, invasive or burdensome procedures additional to those performed under the normal clinical practice.

7.2 Subjects and Sites Numbers

This study will be conducted only on patients with a regular indication for JTIN as per IFU (no off-label use will be included): the nail is indicated for fractures, osteotomies, malunions and non-unions in femur and tibia in pediatric patients suffering from osteogenesis imperfecta. The JTIN is intended to be used in pediatric patients, older than 18 months.
This study includes only one site (monocentric) located in Paris, France. The site was chosen for this study due to the number of subject devices already implanted, and the wideness of the indications covered by the surgeries. The site was also positively evaluated by sponsor for the appropriate qualification and competency of the investigator and of the staff, and availability of facilities and equipment.

The enrollment objective for this study is of 20 evaluable cases (i.e. procedures, see paragraph "Determination of the Sample Size"). For the purposes of this study, a case is defined as one implanted JTIN nail in one treated bone. Each case can be evaluated and recorded from implantation to the last visit for this study (see "Visits and Assessments Schedule" table and "Procedure" paragraph) or up to implant removal if this happens before the last visit. For each case one eCRF record will be created (see "Subject Identifier" paragraph).
Therefore, a single patient at the clinical site can contribute for more than one case e.g.: a patient can have several JTIN each implanted in a different bone, or can have more JTIN implanted in the same bone but at different times.

7.3 Study duration

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

The study duration for each subject implant is approximately 1 year from the date of surgery, according to the visit schedule. Since the subjects will follow standard clinical care of the site

and due to the observational character of the study, the study duration for each subject can be slightly different according to the standard of care.

7.4 Measures to Minimize or Avoid Bias

7.4.1 Blinding and Randomization

The present observational study is an un-controlled, single arm and open-label study therefore, no pre-defined subgroups are planned for the enrolled patients and no stratification, nor randomization, nor blinding procedures will be used.

7.4.2 Subject Identifier

Each time a patient is planned to be treated with JTIN (or has been treated with JTIN after the 1st of January 2022, i.e. retrospectively), he/she is considered potentially eligible for the study and will be screened by the clinical site team to check if they satisfy all inclusion and exclusion criteria. Only if they satisfy the criteria, they will be informed about the study and asked if they want to participate. Patients' non-opposition to the participation to the study and data collection of the single specific implantation of JTIN will be duly documented in medical records. After non-opposition documentation the site staff will create a record in the eCRF that generates a consecutive identification number (ID), related to the procedure. The ID will be registered in the patient log. If the same patient agrees to participate for another JTIN procedure: another ID will be created and a reference to the first ID is made in the dedicated field in the eCRF and in the patient log.

7.5 End of Study (EOS)

The sponsor has the right to close this observational study at any time.
The study will be terminated prematurely in the following cases:

- If the enrolment rate and data collection are significantly delayed;
- If the sponsor will be informed that the activities related to the study are conducted in conflict with the present protocol;
- Any other reason for the sponsor to deem that the prosecution of the study will harm the subjects' health or rights.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 Subject Inclusion Criteria

A patient will be included in the study if:

- is in pediatric age (> 18 month and < 18 years) at the time of surgery;
- is skeletally immature;
- has a diagnosis for OI;
- has a regular indication for surgical intervention with JTIN to treat femoral and/or tibial fractures, osteotomies, malunions and non-unions;
- Patient and/or legal representative is duly informed and doesn't oppose to participation.

8.2 Subject Exclusion Criteria

A patient will not be included in the study who:

- has a medical condition that is a contraindication according to the manufacturer's instruction for use;
- has any conditions that in the Investigator's opinion may interfere with the study execution or due to which the patient should not participate for safety reasons;
- requires the application of, or has already in-situ the application of concomitant devices that cannot be safely removed (except for permitted concomitant devices paragraph);
- is participating in other clinical trials or has taken part in any clinical study in the last 3 months with exception of analytical trials on genetics study related to OI (i.e. studies that do not include an investigational treatment for the patient such as new drugs or other medical devices);
- is likely to be lost to follow up, according to investigator's opinion.

8.3 Subject Withdrawal

Premature discontinuation from the study will occur when an enrolled patient (namely a patient who doesn't oppose to participation) will not undergo the final follow-up visit.
At any time patients may prematurely discontinue from this study for any reason, without explanation and without losing the right to future medical care. The participation of the patient may, at any moment, be terminated by the Investigator as well, if considered appropriate (i.e. the early termination is in the patient's best medical interest).
Patients who prematurely terminate the study are considered as "withdrawal" ("drop out") patients. Possible reasons for withdrawal of a patient from the study are:

- lack of adequate therapeutic response resulting in an unacceptable risk;
- major protocol violation;
- an inclusion or exclusion criteria that becomes invalid;
- serious or intolerable AE preventing the patient from continuing the study;

- refusal of the patient to continue the treatment and/or protocol procedures;
- decision by the Investigator if it would not be in the best interest of the patient to continue the study;
- lost to follow-up;
- death of the patient.

It is understood by all concerned that an excessive rate of withdrawals can render the study not interpretable, therefore, withdrawals of patients should be carefully assessed. However, if a patient decides to withdraw for any reason, all efforts will be made to complete and report the observations as thoroughly as possible in the patient's records and with an end-of-study visit page that will be available in the electronic Case Report Form (eCRF).
Any subject withdrawal, including lost to follow-up, must be traced by the investigator in the patient medical file and in the eCRF, including the possible reasons.
Until such time that the enrolment period is officially closed by the Sponsor, any withdrawn patients may be replaced by recruitment in accordance with the aforementioned protocol to reach the planned number of evaluable cases. The screening number assigned to the withdrawn patient will not be reassigned to another patient.

9. TREATMENT OF SUBJECTS

9.1 Study Investigational Product

The JTIN is indicated for fractures, osteotomies/deformities treatment, malunions and non-unions in femur and tibia in pediatric patients (older than 18 months) suffering from osteogenesis imperfecta. The nail is designed for self-extension, adjusting the length of the device, in order to follow the patient growth as it occurs.
The nail includes the telescopic rod, which consists of two parts (male and female) and bone anchors, which could be either a cap or an epiphyseal screw suitable to the anatomical application or a pin for distal tibial anchorage.
The nail is available in five diameters, identified by the outer diameter of the female part of the rod, 3.5mm, 4.0mm, 4.5mm, 5.0mm and 6.0mm. Each diameter model is available in five lengths, from 100mm up to 350mm.
Application and removal of JTIN can be performed with Orthofix general orthopedic instrumentation.
The implants are made from AISI316LVM stainless steel, conforming to ASTM F138 and ISO-5832.
Please refer to Appendix 1 for the implantable investigational device items catalog number.

Classification and Regulatory status
The JTIN is a CE marked device under European Union MDD 93/42, Annex IX, Classification criteria, as amended by 2007/47/EC)
The JTIN system consists of components classified as IIb, IIa, Ir and Is.

Manufacturer of the Investigational Device
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Instruction for Use (IFU) and Operative Technique (OT)
Being JTIN a market device, the summary of the necessary training and experience needed to use the investigational device is described in the Manufacturer IFU, constantly published and updated by the manufacturer.
The description of the specific medical and surgical procedures involved in the use of the investigational device are described in the OT published and updated by the Manufacturer.
Current IFU and OT will be attached to the study documentation, and can also be found at the following link:

https://ifu.orthofix.it/home/index

Principle of operation of the device
Telescopic intramedullary nails are often used to stabilize fractures, or multiple level osteotomies, whilst permitting continued longitudinal growth.
Based on the intramedullary nailing principle, a nail is inserted into the intramedullary channel of the femur and tibia. Thus, the nail provides a solid connection between bone segments while the bone anchors lock the nail to the bone.

Novel features

- BONE AXIAL ALIGNMENT PRESERVATION

The connection of female part of the rod and drill bit by means of a thread allows the surgeon to drive the nail into the intramedullary channel of the femur, through all the osteotomy sites, without loosening the bone position or without introducing additional hardware into the canal made by drilling.
The drill makes the path for the insertion on the rod which will immediately fill the gap with the female part. Competitor technique needs sequential insertion of male and female parts, this is not optimal because, even if the female part is guided by the male one, a bone dis-alignment leads to a difficult path to follow for the female part.

- RETROGRADE FEMUR APPROACH
  The JTIN is intended to be applied into intramedullary channel of the femur in a retrograde way. This technique is newly used in OI and allows an easier bone alignment and deformity correction. Retrograde approach gives access to both the anchor points of the nail allowing for a better fixation and precise positioning into the knee (whereas is not possible with the current nails on the market).
- SELF LOCKING CAP
  The cap is used as bone anchorage, afterwards it must be connected to the rod in order to work properly. In a similar device as Bailey-Dubow nail the T-piece is connected by plastic deformation of the connection by means of pliers; the JTIN has a self-locking feature that enables the thread to gain stability without further manipulations.
- RETENTION ON DRIVER
  The bone anchors, both the cap and the male part, have a threaded connection for instrument engaging. This allows the screwdriver to firmly grab the implant helping in manipulation and positioning.

Configurations or variants

JTIN includes a number of stainless steel rods, characterized by:

- Diameter (of the female part of the rod)
- Length (of the female part of the rod)

JTIN includes also stainless steel bone anchors to connect the rod to the bone. The bone anchor could be either a cap or an epiphyseal screw or epiphyseal pin, depending on the anatomical application.
Such bone anchors are provided together with the rod ready to be assembled.

Key functional elements

Implantable devices

The JTIN includes three different parts, intended to be assembled together to shape the

device.

Figure 1 - JTIN assembled device

The parts of the JTIN device are:

- Male part, a solid shaft with a built-in bone anchor for bone connection; the bone anchor has the same design of the cap.

- Female part, a hollow shaft designed to host the male part.
- Bone anchors, that could be either one of the following items depending on the application:
    - Cap, a self-locking screw to be connected in a stable way with the female part of the rod at the opposite extremity respect the one the male part is inserted
    - Epiphyseal pin, a threaded pin to be inserted into the distal extremity hole in order to hold the female part of the rod in position

Figure 2 - JTIN device exploded view

Figure 3 - JTIN assembled device with epiphyseal pin option

The male and female parts are intended to be coupled in order to build the telescopic rod. Male and female are free to move both axially and rotationally; this allow the nail to extend axially as the patient growth occurs and rotate for screw the built-in anchor of the male part into the bone.

9.1.1 Packaging and Labelling

This is a post-market and observational study: the investigational medical device labels is provided to the clinical site trough the approved and controlled commercial channels, therefore packaged and labelled according to marketed CE marked devices.

9.1.2 Investigational Products Accountability and Storage

JTIN is provided to the clinical site trough the approved and controlled commercial channels and is part of clinical sites normal equipment repertoire. For this reason a dedicated investigational products accountability is not required. and the storage will be in charge of the site pharmacy as per manufacturer IFU.

9.2 Concomitant Treatments and Rescue Medications

9.2.1 Permitted Concomitant Treatments (Medications and Therapies)

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 JTIN-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 JTIN are permitted.

9.2.2 Contraindications according to Manufacturer IFU

The JTIN system must not be used if a surgical candidate exhibits or is predisposed to any of the following contraindications:

- Active or suspected latent infections in or near the surgical area
- Compromised bone stock, potentially leading to inadequate or unstable fixation of the device
- Suspected or documented metal sensitivity reactions
- Sepsis
- Mental or physiological conditions, who are unwilling or incapable of following postoperative care instructions as it could result in a treatment failure in the intended population

10. STUDY PROCEDURES

10.1 Description of Procedures

Throughout the pre-study meetings, it was assessed and confirmed that the clinical data collected for the study purpose are part of the standard clinical practice for the participating investigational site. As this is an observational study, there are no change or influence on the normal clinical practice of the investigator and patients, and no interference with the local hospital standard of care guidelines and/or the internal therapeutic protocols set and established at the investigational site.
For the purpose of the study, the investigators will screen both:

- patients that have undergone JTIN implantation surgery from the 1st of January 2022
- patients that will receive JTIN implantation surgery (prospectively enrolled);

The investigators shall collect clinical data from the medical record of the subjects, concerning the screening criteria, the surgery (MD application) and 5 following visits: hospital discharge, plaster or immobilization removal, bone consolidation assessment and two follow-up visits.
Data from patients' observation are gathered according to the site practice, therefore timelines and visit frequency presented in this protocol are estimated as average of the site normal clinical practice, actual visit timing for each patient will be performed according to investigators and hospital staff evaluation. The subjects will not undergo additional visit nor non-invasive, invasive or burdensome procedures additional to those performed under the normal clinical practice.
The patients' data will be systematically collected by the investigator in the eCRF provided by Sponsor.

10.2 Visits Description

10.2.1 Visit 0 - Screening

During the screening visit the investigator will evaluate the eligibility of the patients, checking all inclusion and exclusion criteria. Those patients who do not meet any of the criteria must not be enrolled and are considered as screening failures.
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.
For each procedure for which the patient doesn't oppose to participate in for the study, a unique enrolment number will be assigned, which becomes the procedure identification (ID) number as reported in the eCRF and will be registered in the patient log in the ISF. If the same patient agrees to participate for another JTIN procedure: another ID will be created and a reference to the first ID is made in the dedicated field in the eCRF and in the patient log.
Only for the enrolled patient, the Investigator will collect the demographic data and the medical history of the patient including information concerning the limb to be treated with JTIN (baseline) such as the radiographic images, clinical examination (including WBP expressed by qualitative means and ROM as applicable) and the Gillette Functional Assessment questionnaire, according to hospital standard care.

10.2.2 Visit 1 - Surgery (Day 0)

The investigator will collect information regarding the applied JTIN and the surgical intervention itself, including the intraoperative application time of fluoroscopy, previous device removal (if applicable) and eventual blood transfusion. The investigator will also collect X-ray/fluoroscopy images, to assess the treatment outcome, and the medication prescribed after the surgery. From this visit and for the rest of the visits, the Investigator will collect information about adverse events (AEs) and medical device deficiency (MDD).

10.2.3 Visit 2 - Discharge (1 week ± 2 days)

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any.

10.2.4 Visit 3 - Plaster or Immobilizer Removal (2 months ± 2 weeks)

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any. The investigator will also collect x-ray images of the treated limb, clinical examination , and also the weight-bearing protocol assigned to the patient. The bone consolidation will be assessed by surgeon experience and evaluating corticalization of at least three sides of the callus on the radiographs. The WBP for this visit and the following ones will be expressed by qualitative means (e.g. non-weight bearing / partial weight bearing / full weight bearing).

10.2.5 Visit 4 - Bone Consolidation Assessment (5 months ± 2 months)

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any. The investigator will also collect x-ray images of the treated limb, clinical examination will be performed, measure the Knee, Hip, Ankle ROM (as applicable) and also the weight-bearing protocol assigned to the patient. The bone consolidation will be assessed by surgeon experience and evaluating corticalization of at least three sides of the callus on the radiographs.

10.2.6 Visit 5 - 2nd Follow-up Visit (9 months ± 1 month)

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any. The investigator will also perform clinical examination, and also the weight-bearing protocol assigned to the patient.

10.2.7 Visit 6 - 3rd Follow-up Visit (1 year ± 1 month)

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any. The investigator will also collect x-ray images of the treated limb, clinical examination, measure the Knee, Hip, Ankle ROM (as applicable) and also the weight-bearing protocol assigned to the patient. The bone consolidation will be assessed by surgeon experience and evaluating corticalization of at least three sides of the callus on the radiographs. The Gillette Functional Assessment questionnaire is collected and can performed by the investigator in presence or also by telephone or by mail with the parent (or legal representative) in a different day from the visit, according to hospital standard care.

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Adverse Events

11.1.1 Definition of Adverse Event (AE)

Based on ISO 14155:2020, an “adverse event” is defined as untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Conditions or diseases diagnosed before subject inclusion in the study that are chronic but stable should not be recorded on AE pages of the CRF but they are a part of the Medical History. Chronic diseases which are diagnosed during subject participation in the study shall be recorded as AE/SAE.

11.1.2 Definition of Serious Adverse Event (SAE)

In accordance with ISO 14155:2020, a Serious Adverse Event (SAE) is an adverse event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that either resulted in users, or other persons as defined by one or more of the following:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function including chronic diseases, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or, a congenital abnormality, or birth defect including physical or mental impairment.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a serious adverse event. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions if not associated with the new occurrence of AE/SAE
- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study if not associated with the new occurrence of AE/SAE
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study if not associated with the new occurrence of AE/SAE.

11.1.3 Definition of Adverse Device Effect (ADE)

An adverse device effects describes an adverse event related to the use of an investigational medical device.
This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
This includes any event resulting from use error or from intentional misuse of the investigational medical device.

11.1.4 Definition of Serious Adverse Device Effect (SADE)

SADE are any adverse device effect that has resulted in any of the characteristics of a serious adverse event (see above).

USADE are serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

11.1.5 Possible Adverse Device Effect according to Manufacturer IFU

List of possible Adverse Device Effect expected from Manufacturer IFU (ASADE):

- Non-union, delayed union or malunion
- Superficial infection
- Deep infection
- Bending, breakage or migration of the device
- Bone fracture during or after treatment
- Damage to bone vascularization (e.g. proximal femoral epiphysis)
- Damage to surrounding tissues due to surgical trauma
- Pain, discomfort or abnormal sensations due to the presence of the device
- Possible lesion to the growth plates
- Residual deformities, persistence or recurrence of the initial condition subject to treatment
- Wound healing complications
- Stiffness at surgery site
- Problems related to telescopic functioning
- Events caused by intrinsic risks associated with anesthesia and surgery

11.1.6 Possible ADE incidence, mitigation, and treatment

The incidence of the possible ADE identified by the Manufacturer is not available for investigational device (JTIN) because the present study is the first systematic clinical data collection on the device. The following table provides a pooled complication rates from published literature.

Surgical revision	22.22% - 50% [Rosenberg, 2018]; [Sarikaya, 2019]; [Scollan, 2017]
Bone deformity	4.3% - 30% [Lee K, 2015]; [Scollan, 2017]; [Shin, 2018]
Repeat fractures	11.11% - 37.29% [Popkov, 2020]; [Rosenberg, 2018]; [Sarikaya, 2019]; [Scollan, 2017]; [Shin, 2018]
Hardware displacement/ breakage/bending	32% - 33% [Lee K, 2015]; [Scollan, 2017]; [Shin, 2018]
Non-union/delayed union	8.47% - 36% [Lee K, 2015]; [Scollan, 2017]; [Shin, 2018]
Osteomyelitis (infection)	3.85% [Rosenberg, 2018]
Limited/absent telescoping	11.11% - 40% [Rosenberg, 2018]; [Sarikaya, 2019]

Repeat fractures is the most commonly reported complication with the use of intramedullary nails, although that might be due to the inherent bone fragility associated with OI.
Among the hardware-related complications, rod migration was the most reported one that might lead to an increased rate of surgical revision.

The Manufacturer has developed the novel feature the JTIN system to mitigate these two more commonly reported complications. JTIN system features and the retrograde technique, newly used in OI, allow to obtain stable bone fixation and an easier bone alignment and correct deformities (see chapter 9.1 Study Investigational Product “Novel Features”).

All AE/ADE and any device deficiency will be treated by the clinical center according to the clinical standard practice of the hospital, since this is an observational study. All events will be recorded and reported in the case report form as appropriate, see following paragraphs.

11.1.7 Relationship between an AE/SAE and the use of the medical device

All AE/SAE will be judged by both the reporting Investigator and the sponsor as having a reasonable causal relationship to the investigational medical device. The relationship between the AE/SAE and the investigational medical device is considered

- **Certain** when the AE/SAE occurs in a plausible time relation to the application of the device and cannot be explained by a concurrent disease or other devices, drugs or chemicals. The response to withdrawal of the device (de-challenge) should be clinically

plausible. The event must be definitive using a satisfactory re-challenge procedure if necessary;

- **Possible** when the AE/SAE occurs with a reasonable time relation to the application of the device, but it could also be explained by a concurrent disease or other devices, drugs or chemicals. Information on device withdrawal (de-challenge) may be lacking or unclear;

The AE/SAE is **Not Related** to the use of the investigational device in case of:

- existence of a clear alternative explanation, and/or
- unreasonable temporal relationship between application and/or
- non plausibility.

11.1.8 Medical Device Deficiency (MDD)

A “device deficiency” is defined as an “Inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.” A Medical Device Deficiency (MDD) is a device deficiency related to the device and ancillary tools used for the clinical investigation (for the present study it is the JTIN and ancillary tools used for implantation and extraction, see Appendix 1 for ancillary tools) and, when applicable, related to the comparative devices as well (for this study the comparative devices is not applicable).
Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

11.1.9 Incident

Incident means any malfunction or deterioration in the characteristics or performance of a device made available on the market and related ancillary tools used for implantation and extraction, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect; Incidents will be followed according to routine materiovigilance requirements.

11.1.10 Procedures for Reporting and Recording AE, SAE and Medical Device Deficiencies

The investigator will follow the standard clinical practice to record data in the medical file. He/she will follow the national applicable vigilance procedures for any applicable case of AE or incident, and the manufacturer instruction to report any MDDs or AE as appropriate.

In addition to the above-mentioned requirements, the investigator will also record the AEs and MDDs in the eCRF. For both cases the investigator, when reporting the event in the eCRF will describe:

- date of the event;
- treatment;
- resolution;

- whether or not it is Serious and
- whether or not it is related to the use of the investigational device and the related procedure

When applicable, the investigator should also provide any available information and diagnostic measurements (laboratory test, X-ray etc) related to the AE and store it in the eCRF.

11.1.11 Notification deadlines

Notification to Sponsor
Serious MDDs and SAEs related to the investigational medical device and related procedure must be notified by the Investigator to the Sponsor through the appropriate form (Safety Reporting Form PO218-02) provided with the study documentation immediately, or within 2 calendar days from awareness, at the latest. This timeline applies only to prospective investigational data.
Please email the completed Safety Reporting Form Device deficiency and Compliant to Orthofix Srl at the following:

Safety Contact Information

safetyclinicalstudiesintl@orthofix.com

complaintintl@orthofix.com

Notification to Authorities

All SAEs related to an investigational procedure leading to death or imminent threat to death, a serious injury or disease, requiring a rapid corrective action must be notified by the sponsor to Competent Authority immediately or within 2 days at the latest.

Other SAEs must be notified by the sponsor to Competent Authority immediately or within 7 days at the latest.

The same guidance applies to complementary information related to these events.

In addition, as this is a PMCF observational study regarding a CE-marked device, the sponsor will comply with Articles 87 to 90 of MDR and detailed in MDCG 2023-3 (published in February 2023)

According to mentioned articles and guidelines, the sponsor will report to the competent authority all incidents that will occur during the use of the medical device covered by this study by specific reporting. For serious incidents with the most urgency, the reporting will be through Manufacturer Incident Report MIR 7.2.1 and sent to the competent authority with the most urgency and in any case no later than 10 days as well as to the local EC. For all other incidents, this timeline is within 30 days.

12. STATISTICS

12.1 Statistical and Analytical Plans

Clinical data collected throughout the study will be analyzed by descriptive statistics to assess the study objectives. Descriptive statistics will be provided in summary tables according to the type of variable summarized:

- Quantitative variables will be summarized by using n (sample size), arithmetic mean, standard deviation (SD), median, minimum and maximum.
- Categorical variables will be summarized by using frequency distribution and percentages.

The design of the proposed study does not involve randomization, so no pre-defined subgroups of subjects are planned to be enrolled.
For time-to-event variables, cumulative freedom from event will be evaluated using Kaplan-Meier (KM)
method. The degree of uncertainty will be expressed with 95% confidence limits (calculated per the method proposed by Greenwood). KM graphs will be presented along with the number of case-at-risk at exact time points.
Unless otherwise specified, the significance level used for other statistical testing (for descriptive purposes) will be 0.05 and two-sided tests will be used.
The Statistical Analysis Plan (SAP) could be issued before database lock with more technical and detailed elaboration of the principal features of statistical analyses. Any deviations from the original statistical plan (including unplanned analyses) will be documented in the Clinical Study Report.

12.1.1 Population(s) of analysis

The following populations will be defined:

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

12.1.2 Efficacy, Safety and Other Variables

12.1.2.1 Efficacy Variables

Efficacy variables will include:

1. Bone union achievement;
2. Post-treatment fracture free survival.

12.1.2.2 Safety Variables

Safety variables will include:

1. Any complications;
2. Re-operation/Revision;
3. Implant survival;
4. Any expected/unexpected AE (see Section 11.1.5 for details).

12.1.2.3 Other Variables

All variables reported in the Table above (Section 4.1) will be included, as per scheduling assessment.

12.2 Statistical Evaluation

12.2.1 Evaluation of Safety

To evaluate the primary safety objective of the analysis, the number of all AEs, SAEs and MDDs and the number and the percentage of implants with subsequent AEs, SAEs and MDDs will be summarized (primary endpoint), together with the information about relationship (certainly or possibly related) to JTIN.

In addition, a similar analysis will be performed at subject level (number and percentage of subjects with at least one implant with subsequent adverse events).
Furthermore, as secondary safety endpoint, the implant survival rate will be evaluated and reported as percentage of implants with no exchanged nails up to 1 year follow-up.

12.2.2 Evaluation of Efficacy

The first efficacy endpoint (Bone union achievement) will be analyzed reporting the number and the proportion of procedures with bone union achieved (Success) together with the relative 95% confidence interval.

The second efficacy endpoint (Post-treatment fracture-free survival) will be analyzed reporting the number and the proportion of procedures with fracture(s) occurred in the treated bone up to 1 year follow-up together with the relative 95% confidence interval.

The cumulative freedom from fracture will be also evaluated using Kaplan-Meier (KM) method, the degree of uncertainty will be expressed with 95% confidence limits (calculated per the method proposed by Greenwood) and a KM graph will be presented along with the number of case-at-risk at exact time points.

12.2.3 Exploratory Analyses

Change in Gillette Functional Assessment Questionnaire from Screening to bone consolidation assessment visit and to 1 year follow up will be analyzed by means of

descriptive statistics as a continuous variable. Pre-post comparisons will be performed by means of paired t-test.

12.3 Determination of the Sample Size

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

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

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

12.4 Interim Analysis

No interim analysis is planned.

12.5 Dictionaries

Medical/Surgical history, concomitant diseases and AEs will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary and reported in separate tabulations. Frequency distributions and percentages will be summarized by System Organ Class (SOC) and Preferred Term (PT).

Prior and/or concomitant medications will be coded using World Health Organization Drug Dictionary and reported in separate tabulations. Frequency distributions and percentages will be summarized by Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.

13. ETHICS AND REGULATORY REQUIREMENTS

13.1 Approval

As a PMCF observational study conducted on a CE-marked medical device used according to its intended use with no additional procedure, this study doesn't fall within the scope of MDR 2017/745 nor French Jardé law on Research that implies human beings.

As Data Controller, the sponsor commits to comply with GDPR- 679/2016 and Title II Chapter 3 Section 3 of French Data Protection law of January 6th, 1978 regarding data processing.

According to Article 73 of French Data Protection law, considering that data processing related to this study complies with CNIL's reference methodology MR-004, for which the Sponsor, as Data Controller, has previously registered a compliance commitment with the French data protection body, authorization from CNIL is not mandatory for data processing and study start.

Sponsor has also submitted the study to APHP Research Ethical Committee.

13.2 Subject Information and Non-opposition

The screened patients, who has undergone JTIN implantation according to the standard-of-care and comply to all inclusion and exclusion criteria, should not oppose to participate in this study. Prior to being enrolled into the study, each patient, according to the age range, and his/her parents/legal representative, will be informed by the Investigator or his/her designee regarding the purpose of the study and the clinical data that will be collected. The Investigator will deliberate that, considering this is an observational study, there are no additional foreseeable risks and potential benefits resulting from study participation compared to normal clinical practice.
Each patient/parents/legal representative will be informed by the Investigator that he/she is free to refuse to participate in the study and, if he/she chooses to participate, that he/she may withdraw from the study at any time without providing reasons. In addition, the patient/parents/legal representative will be informed that, in some necessary cases, the Investigator may prematurely terminate their participation providing an appropriate reason.
The Investigator will provide the patient/parents/legal representative with her/his contact details in case they need further information after inclusion.
Each patient/parents/legal representative will be informed that his/her medical records will be Subject to review by the Sponsor representatives and may be subject to review from auditor and regulatory authorities.
The data collected during the treatment period, will be systematically entered by the investigator in eCRF.

The patients/parents/legal representative will be informed during their participation to the study about any new information eventually available about the medical device by the investigator.

Patient/parents/legal representative's non opposition will be documented in concerned patient's medical records and certified by Investigator or his/her designee.

13.3 Subject Confidentiality

All information and data concerning patients participating in this study will be considered confidential according to the requirements of EU GDPR regulations and national applicable regulations. The Information sheet shall describe the process of subject data protection in details.

Each enrolled subject will be assigned to a unique study ID number for each procedure, which is pre-configured in the EDC and all data collected in EDC will be identified only by this ID number. Records of the subject/study ID number relationship will be maintained only by the study center.

The study ID number is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any study document entered in EDC. In the event a subject's name is included for any reason, it will be blinded as applicable.

Confidentiality of data will be observed by all parties involved at all times throughout the study. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

14. STUDY MANAGEMENT AND ADMINISTRATION

14.1 Supplies

After the required approval will be obtained before the site will be initiated, the sponsor, also through its appointed partners, will provide the site with the following supplies:

- A paper and electronic copy of this protocol;
- Copies of the Information sheet to be provided to the enrolled Subjects;
- Blank copies of the non-opposition form to be signed by the Investigator or his/her designee;
- The Investigator Site File (ISF) containing all the study related documents;
- An eCRF platform and the credential to enter the system to upload clinical data.

14.2 Monitoring

The sponsor planned to perform a 100% source data verification (SDV) on inclusion/exclusion criteria and on the endpoints' variables, both primary and secondary. On the remaining data the SDV will be performed by random spot check (20% of the total visits entered in the eCRF). Before each visit the monitors will contact the investigator/center to schedule the visit and will send a written confirmation and the related agenda.
In order to fulfill its responsibility of assuring the proper conduct of the study regarding adherence to the protocol and the completeness and accuracy of the data recorded on the case report forms, the sponsor planned to perform at least the following monitoring visits:

- Site Initiation Visit (SIV), to be performed after EC/administrative approval;
- 4 monitoring visits throughout the life phase of the study;
- Close Out Visit (COV), after the last patient's data are entered into eCRF.

A detailed description of the monitoring activities will be provided in a separate Monitoring Plan. In case of need the investigational site is subjected to additional monitoring visits. The Investigator and/or study staff is expected to be available for at least a portion of the monitoring visit to answer to questions and to provide any missing information.

14.3 Direct Access to Source Data/Documents

With all efforts to ensure that patients' pseudo-anonymity and confidentiality is respected, the Investigator will permit the clinical monitors to have direct access to all study records, including hospital records, all source documents and ISF.

14.4 Audit and Inspection

There may be a possibility that the Quality Assurance Department of the sponsor or the Regulatory Authorities may audit or inspect the site to verify compliance to protocol, procedures and applicable regulations.

The investigator will permit to be audited/inspected by sponsor personnel and/or Regulatory Authorities during and/or after the study has been completed.

14.5 Adherence to Protocol

Protocol deviations will be reported to the sponsor who will assess their significance (Major and Minor) with regards to the impact on the rights, safety, and well-being of human subjects, and to the impact on quality and data integrity. All deviations will be reported and discussed in the study report.

In case of a protocol amendment, before the suggested modifications will be implemented, the sponsor will notify the new version of the protocol to the relevant IEC and authorities, specifying whether the modifications are substantial/not-substantial and, if applicable, will put the study on hold until the re-approval will be obtained, if applicable.

14.6 Data Handling and Retention

The sponsor and the investigator assume the responsibility to assure that the clinical data will be collected according to the CIP requirements (no additional data will be collected), local laws and obligations and the World Medical Association Declaration of Helsinki. The clinical data obtained as a result of this study is considered confidential between the site and the sponsor: disclosures to third part are prohibited or, if necessary for example to perform statistical analysis with contracted vendors, will be protected by non-disclosure agreements.

Before the Site Initiation Visit, the sponsor will provide an eCRF system (Castor) that is validated according to applicable laws and regulations, including 21 CFR Part 11, EU Annex 11, General Data Protection Regulation (GDPR), HIPAA (US), ISO 9001 and ISO 27001. The Sponsor will provide training to the Investigators/CRA about the data entry procedures and queries solving. The clinical data entered in the eCRF must come from the source data, that is all information in original (or certified copies) reported in source documents (for example: patients' clinical records, records of clinical findings, investigator's observations/assessment).

The investigator assumes the responsibility to assure that the last data will be entered within 1 month after the last patient last visit (including all queries resolution).

The investigator will have to keep all study related documentation for the longest possible duration, but at least for 15 years after the completion or premature termination of the study. No data should be destroyed without agreement with the sponsor. The Sponsor will maintain all documentation pertaining to the study for the lifetime of the product.

Sponsor and investigators shall take measures to prevent accidental or premature destruction of these documents and they may rely on a third part for documents retention by a non-disclosure agreement to protect data confidentiality.

14.7 Clinical Study Report

The clinical study report shall be completed by the sponsor, or a designed delegate by the means of a non-disclosure agreement, even if the study will be terminated prematurely, only after:

- all queries concerning the eCRF will be closed;
- the database will be locked;
- the statistical report will be written and approved.

The sponsor will draft the clinical study report after the finalization of the statistical report. The clinical study report will be reviewed and approved by the investigator and, as soon as available, shall be provided to the relevant IEC and authorities (when applicable).

14.8 Insurance and Liability

No additional procedures for the patients nor for the investigational team members are planned for the present observational study with respect to the normal clinical practice, that actually comprises a retrospective and prospective data collection. The sponsor, therefore, is not requested to put in place an additional dedicated liability insurance covering this study.

14.9 Financial Disclosure

Assumed this is a sponsored study, after the relevant IEC and authority approval/authorization the sponsor will put in place with the hospital administration of the site an agreement that will allow to pay the involved department for study execution.

The information regarding Financial Disclosure of the Investigator will be collected and retained in the Trial Master File.

14.10 Publication

The sponsor and the investigator intend to compile a comprehensive publication of study results in a peer review journal, within 6 months from study completion or early termination, appropriately addressing contributions of co-authors.

Co-authors will be designated by the investigator (study staff at the hospital e.g. sub-investigator) and by the sponsor from the staff involved in the design and conduction of the study.

The sponsor recognizes the right and interest of co-authors, to scientifically publish the results obtained from the study for non-commercial purposes, even if the effects ascribed to the investigational product fail to materialize. All article or scientific presentation from investigator and co-authors can be published only after the first publication of the results by the sponsor.

The sponsor, together with the investigator, reserve the right to publish and present the results of this study at scientific congresses, to submit these clinical trial data to national and international Regulatory Authorities.

At least 30 days before any publication or presentation of study results, co-authors agree in submitting a manuscript/abstract of the intended publication or presentation to the sponsor for review. The sponsor will provide its revision within 15 working days. Proposals for changes and modifications raised by sponsor will be taken into consideration by the participating Investigators if such proposals do not interfere with the scientific nature and content of the publication.

The identity of the sponsor and the nature of his contribution to this study shall be disclosed in any publication or presentation.

The sponsor, according to current EU regulation (MDR 2017/45) and guidelines (ISO 14155) is responsible to register the study in a publicly accessible database. The current status and details of the study is publicly accessible on ClinicalTrials.gov at the registration nr. NCT05612139.

15. REFERENCES

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16. APPENDICES

16.1 Appendix 1: Investigational Device items catalog number

Sterile version:

CATALOG NUMBER	DESCRIPTION
99-67735100	JTIN TELESCOPIC NAIL L100MM D3.5MM STERILE
99-67735120	JTIN TELESCOPIC NAIL L120MM D3.5MM STERILE
99-67735130	JTIN TELESCOPIC NAIL L130MM D3.5MM STERILE
99-67735140	JTIN TELESCOPIC NAIL L140MM D3.5MM STERILE
99-67735150	JTIN TELESCOPIC NAIL L150MM D3.5MM STERILE
99-67740130	JTIN TELESCOPIC NAIL L130MM D4.0MM STERILE
99-67740155	JTIN TELESCOPIC NAIL L155MM D4.0MM STERILE
99-67740180	JTIN TELESCOPIC NAIL L180MM D4.0MM STERILE
99-67740205	JTIN TELESCOPIC NAIL L205MM D4.0MM STERILE
99-67740230	JTIN TELESCOPIC NAIL L230MM D4.0MM STERILE
99-67745160	JTIN TELESCOPIC NAIL L160MM D4.5MM STERILE
99-67745175	JTIN TELESCOPIC NAIL L175MM D4.5MM STERILE
99-67745190	JTIN TELESCOPIC NAIL L190MM D4.5MM STERILE
99-67745205	JTIN TELESCOPIC NAIL L205MM D4.5MM STERILE
99-67745230	JTIN TELESCOPIC NAIL L230MM D4.5MM STERILE
99-67750250	JTIN TELESCOPIC NAIL L250MM D5.0MM STERILE
99-67750275	JTIN TELESCOPIC NAIL L275MM D5.0MM STERILE
99-67750300	JTIN TELESCOPIC NAIL L300MM D5.0MM STERILE
99-67750325	JTIN TELESCOPIC NAIL L325MM D5.0MM STERILE
99-67750350	JTIN TELESCOPIC NAIL L350MM D5.0MM STERILE
99-67760250	JTIN TELESCOPIC NAIL L250MM D6.0MM STERILE
99-67760275	JTIN TELESCOPIC NAIL L275MM D6.0MM STERILE
99-67760300	JTIN TELESCOPIC NAIL L300MM D6.0MM STERILE
99-67760325	JTIN TELESCOPIC NAIL L325MM D6.0MM STERILE
99-67760350	JTIN TELESCOPIC NAIL L350MM D6.0MM STERILE

Non-sterile version

CATALOG NUMBER	DESCRIPTION
67735100	JTIN TELESCOPIC NAIL L100MM D3.5MM
67735120	JTIN TELESCOPIC NAIL L120MM D3.5MM
67735130	JTIN TELESCOPIC NAIL L130MM D3.5MM
67735140	JTIN TELESCOPIC NAIL L140MM D3.5MM
67735150	JTIN TELESCOPIC NAIL L150MM D3.5MM
67740130	JTIN TELESCOPIC NAIL L130MM D4.0MM
67740155	JTIN TELESCOPIC NAIL L155MM D4.0MM
67740180	JTIN TELESCOPIC NAIL L180MM D4.0MM
67740205	JTIN TELESCOPIC NAIL L205MM D4.0MM
67740230	JTIN TELESCOPIC NAIL L230MM D4.0MM
67745160	JTIN TELESCOPIC NAIL L160MM D4.5MM
67745175	JTIN TELESCOPIC NAIL L175MM D4.5MM
67745190	JTIN TELESCOPIC NAIL L190MM D4.5MM
67745205	JTIN TELESCOPIC NAIL L205MM D4.5MM

67745230	JTIN TELESCOPIC NAIL L230MM D4.5MM
67750250	JTIN TELESCOPIC NAIL L250MM D5.0MM
67750275	JTIN TELESCOPIC NAIL L275MM D5.0MM
67750300	JTIN TELESCOPIC NAIL L300MM D5.0MM
67750325	JTIN TELESCOPIC NAIL L325MM D5.0MM
67750350	JTIN TELESCOPIC NAIL L350MM D5.0MM
67760250	JTIN TELESCOPIC NAIL L250MM D6.0MM
67760275	JTIN TELESCOPIC NAIL L275MM D6.0MM
67760300	JTIN TELESCOPIC NAIL L300MM D6.0MM
67760325	JTIN TELESCOPIC NAIL L325MM D6.0MM
67760350	JTIN TELESCOPIC NAIL L350MM D6.0MM

Ancillary Tools

Part#	JTIN Instrument	Picture
99-671001	JTIN INSTRUMENT SET STERILE	
99-16710000	JTIN SCREWDRIVER STERILE	
99-16730000	JTIN NAILS GAUGE D3.5 AND 4.0MM STERILE	
99-16740000	JTIN NAILS GAUGE D4.5 TO 6.0MM STERILE	
166260	BONE AWL*	
166955	NAIL INSERTER*	
W1003	WIRE CUTTER*	

*Optional instruments

Part#	JTIN Extraction Set	Picture	
99-671002	JTIN PIN EXTRACTION SET NAIL D3.5MM STERILE		
99-671003	JTIN PIN EXTRACTION SET NAILS D4.0MM TO 6.0MM STERILE		

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