Clinical Investigation Plan

BIOABSORBABLE INTRAMEDULLARY NAIL FIXATION OF FOREARM FRACTURES IN CHILDREN

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Change History

Version	Date	Description
1	11/2009	Initial version
2	11.11.2009	
3	19.2.2010	Adding of signatures and corrections of version and dates
4	17.3.2011	• Updating of investigation sites and team • Adding of two pilot operations per investigation site • Updates of inclusion criteria concerning the subjects' age and exclusion criteria concerning delay time of operation • Adding of 2 mm bioabsorbable IM nail to the device list for the young subject with narrow bone cavity • Additional instructions to the surgical procedure • Schedule of MRI imaging
5	***5.2.2018***	• updated study group and coordinating researcher • power analysis re-performed and N of study and control cases changed • objectives were focused • typographical errors were corrected

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Abbreviations

AE	Adverse Event
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AP	Anterior-Posterior –direction
BMI	Body Mass Index
CIP	Clinical Investigation Plan
CRF	Case Report Form
Galeazzi fracture	middle to distal third radius fracture, with intact ulna, and disruption of the distal radioulnar joint
IM	Intramedullary Nail
Monteggia fracture	proximal ulna fracture with associated dislocation of the radial head
MRI	Magnetic Resonance Imaging
ORIF	Open Reduction and Internal Fixation
PLLA	Poly-L-lactide
ROM	Range of Motion
RUS	Region Under Study
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operation Procedure
SR	Self-reinforcing, an orientation method applied to increase the strength of the bioabsorbbale implant materials, e.g. polylactide => SR-PLLA
TEN	Titanium Elastic Nail
VAS	Visual Analogue Scale

Identification

Clinical Investigation Plan Title: Bioabsorbable Intramedullary Nail Fixation of Forearm Fractures in Children

Ref No: A228-CIP-1

Version No: 5

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Synopsis

Name of Sponsor:

Bioretec Ltd.

Name of Medical Device:

Bioabsorbable Intramedullary Nail

Title of Study:

Bioabsorbable Intramedullary Nail Fixation of Forearm Fractures in Children

Investigators:

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Study Centres:

- **Oulu University Hospital,** Department of Children and Adolescents
- **Central Hospital of Päijät-Häme**, Department of Surgery, Unit of Paediatric Surgery

Studied Period (weeks): 52 (follow up 2 years)

Date of First Enrolment: 2010

Date of Last Completed: ***2018***

Objectives:

Primary objective: Clinical outcome of the fracture treatment is equal between patients treated by the new bioabsorbable medical device and by standard of care using a titanium alloy device. This will be assessed by functional and clinical outcome measuring range of motion of forearm, wrist and elbow and pain assessment at two-years' follow-up.

Secondary objective: The new medical device (bioabsorbable intramedullary nail) is at least as good as the routinely used device (elastic stable titanium alloy intramedullary nail) in forearm fracture treatment to achieve a level of reduction and stabilisation that is appropriate to the age of the child. This will be assessed by radiological outcome and determination of bony union formation and alignment in the healing forearm fracture using radiographic methods; further, soft-tissue and bone-tissue reactions are to be evaluated by MRI.

Methodology:

The fracture is fixed using the new medical device (bioabsorbable intramedullary nail) or the standard titanium intramedullary nail.
Number of Patients: At most 2 pilot operations / study centre + Planned 13 operations required for analysis; Total 35 patients to be enrolled, appreciating the potential drop-outs.
Diagnosis and Main Criteria for Inclusion and Exclusion: Diagnosis: Children with an unstable midshaft (diaphyseal) forearm (radius and/or ulna) fracture. Main inclusion and exclusion criteria: The subject and/or guardian has signed and dated the informed consent, the subject is 5 to 16 years of age, the subject has no previous fracture or infection of the study region, no metabolic bone disease, no systematic disease or medication affecting bone quality or resistance to infection.
Medical Test Device installation and identification: The device is surgically implanted. The batch of device is identified by test device name, packaging date and clinical investigation number A2228-CIP-1.
Duration of Treatment: The follow-up of the patients will be 104 weeks (2 years). The control device will be removed 6 months after operation. The bioabsorbable device is expected to retain its mechanical functionality for at least 8 weeks, while the complete bioabsorption of the device in human body is expected to take place within approx. 2 years.
Criteria for Evaluation: Repeated examination of functional, clinical and radiographic outcome, and bone union formation by range of motion measurement, radiography (plain radiographs). Magnetic resonance imaging for a randomly selected subgroup of at least 10 patients treated by test device, general questionnaires. **Efficacy:** The success of fixation will be determined by radiographic measurements in comparison between the immediate postoperative state and 6, 12 and 26 weeks after surgery. **Safety:** Continuous evaluations of safety parameters and specific evaluations of adverse events and serious adverse events will take place at each postoperative study visit. The safety variables to be evaluated include adverse events, findings from physical and radiographic examinations, subjective reports of pain and functional outcome assessments.
Statistical Methods: The primary variable will be analysed using an analysis of variance model for repeated measurements. Treatment differences with 95% confidence intervals will be calculated from the model.

Identification of the Investigational Device

Investigational devices for intramedullary nail fixation are manufactured by Bioretec Ltd. Devices are intended for forearm fracture repair of radial and/or ulnar shaft. The main purpose of the device is to achieve a level of reduction and stabilisation of fracture that is appropriate to facilitate the uneventful bone healing, thus restoration of the pre-trauma anatomical structure, taking into account the age of the child. In addition, the need for the second operation to remove hardware will be obviated by the investigational devices.

Devices are made of bioabsorbable oriented high-strength poly(lactide-co-glycolide) (PLGA) 85:15. The diameter of the IM nails is 2.0 mm, 2.7 mm or 3.2 mm. The nails are 400 mm long and in the tips of the nails there are x-ray positive markers. The high strength of IM nails is result of special orientation techniques applied in the manufacturing of the products at Bioretec Ltd. The corresponding shorter product, ActivaPin™ is registered product, which has been on the EU and US markets already several years.

Prior training in the insertion techniques of bioabsorbable devices is recommended.

Identification of the Control Device

Commonly used titanium elastic nail (TEN) manufactured by SynthesDePue Inc. is used as a control device in this study. According to routine clinical practices, the control device LOT number is documented into CRF. The main purpose of the device is to achieve a level of reduction and stabilisation of fracture that is appropriate to facilitate the uneventful bone healing, thus restoration of the pre-trauma anatomical structure, taking into account the age of the child. Prior training in the insertion techniques of TEN nails is recommended.

Preliminary Investigations and Justification of the Study

The purpose of this prospective, randomized clinical trial is to assess the efficacy and safety of a bioabsorbable device in fixation of forearm fracture patients. As the primary endpoint, the bioabsorbable intramedullary nail is expected to act as efficiently as the routinely used TEN nails in stabilization of forearm fractures in pediatric patients with unstable radius and/or ulna fractures.

Literature Review

Closed reduction and plaster cast immobilization provides in most cases of children's forearm fractures sufficient stability for an uneventful healing of the fracture and gives a satisfactory end result. [1-5] The satisfactory results are achieved due to rapid healing and remodelling of angulations in children.
However, in cases of

- unstable fractures (e.g. midshaft diaphyseal forearm fractures),
- fractures with unacceptable alignment and fracture dislocations,
- open fractures,
- segmental fractures,
- proximal fractures that will not remodel as predictably and
- those with associated neurovascular compromise

an operative treatment is often mandatory to avoid residual deformity with permanent loss of forearm rotation. [1, 3, 6-9] Remodeling will not correct rotational deformities of the distal third of the forearm; for that reason, rotational deformities must be often treated operatively. [2] In addition, in an older child ability for fracture remodeling and correction of deformity is not as effective as in a younger child, therefore the operative treatment of displaced forearm fractures is often recommended in children older than 10 years of age and in younger children when conservative treatment fails.

Effective operative alternatives of unstable fractures include open reduction and internal fixation (ORIF) with plates and screws or mini-open reduction and intramedullary (IM) nailing. [1, 8-10] The choice of fixation usually is a matter of surgeon preference.

Plate fixation allows anatomic reduction and early motion with most studies showing good outcomes in the pediatric population. However, plate fixation requires a large surgical approach and smaller children may have bones that are too narrow to accommodate a plate. [8] In addition, incision for a plate fixation is greater than that required for IM nailing. In contrary to TEN nailing if plate fixation is applied the injured area of bone is exposed. This may also have a negative effect on the healing of the fracture by disturbing the haematoma and callus formation and increase complication possibilities, like infection. Plate removal is also associated with significant complications, such as nerve injury, and in addition, the removal of plate may be difficult due to scarring and bone growth over the plates. [9]

Flexible intramedullary nailing of pediatric forearm fractures has shown also excellent results. [2, 7, 9-12] The advantages of closed reduction and IM nailing include a minimally invasive

form of treatment of pediatric fractures and avoiding large incisions, shorter procedures, and ease of hardware removal, with a lower refracture rate compared with plates. [2, 10] Usually, TEN nails can be placed without disturbing the fracture site in some cases; however, in others the fracture is open, reduced, and fixated with the nail. Titanium elastic nails are a popular choice, but rush rods and Steinman pins/Kirschner wires also are used. [7, 10-13]

The inherent disadvantageous of these metallic devices are stress shielding phenomenon, pain and local irritation. [14, 15] Retained metallic implants provide an attractive and stable host surface for intraoperatively derived bacteria and possess the risk of endogenous infection. Release of metallic ions from these implants has been documented, though the long-term effects of these are not yet known. Because of these reasons in the use of metallic IM nails there is also need for a second operation to remove hardware after the bone has healed. The removing of IM nail is performed when the full healing has occurred, usually 4 - 6 months after operation, but the nails are removed earlier if a bridging callous is present and the hardware is prominent or painful. Generally, the removal operation of metallic devices has significant economic implications, including the costs of the procedure as well as possible work time lost by the parents accompanying the removal operation. Especially for the pediatric patients and their parents the removal operation causes needless discomfort and concern. The removal operation also always possesses the risk of anesthesia complications and infection. The problems presented above have led to the development of bioabsorbable IM nails.

Bioabsorbable devices and IM nails

During the last decades bioabsorbable implants made utilizing orientation techniques have gained a wide acceptance in the treatment of various cancellous bone fractures and osteotomies. Due to their complete biodegradation character the need for a second operation for removal of the device is overcome and long-term interference with children's growing skeleton is avoided. These implants also offer the advantages of gradual load transfer to the healing tissue, reduced risk of peri-implant osteoporosis and infection. An important aspect is that these implants do not interfere with clinical imaging after surgical implantation. [15]

In paediatric orthopaedics Bostman et al. showed that self-reinforced absorbable rods were suitable for fixation of physeal fractures in children. [16] In 1991, Hope et al. had compared the self-reinforced absorbable rods with metallic fixation of elbow fractures in children. [17] Partio et al found SR-PLLA screws firm enough for fixation of subtalar extra-articular arthrodesis in children. [18] Bioabsorbable fixation technique for pediatric olecranon fractures has been described, with the advantage of avoiding reoperation to remove hardware. [19]

Favorable results on treatment of forearm fractures by bioabsorbable intramedullary nails was gained already in the 1990. [20-22] In that study the poly-L-lactide (PLLA) IM-rods seemed to be a viable option in the treatment of children's fore-arm fractures, based on 3,5 years follow-up carried out in this study.

Bioretec's ActivaPin™ products have gained excellent clinical outcome in the different indications of orthopedics and trauma surgery. The modified (lengthened) bioabsorbable devices for fixation of children's unstable forearm fractures are manufactured by Bioretec Ltd based on ActivaPin™ technology. Devices are intended for repair of children's unstable forearm (radius and/or ulna) fractures. In addition to extended length an X-ray marker has been added to the tip of the implant to facilitate the similar insertion technique applied for TEN nails, which utilizes fluoroscopy to monitor the position of the tip of the implant intra-operatively. The main purpose of the device is to stabilize diaphyseal forearm fractures of children in the alignment of the repositioned state for at least 6 weeks in the presence of appropriate immobilization and to obviate the need for second operation to remove the hardware. The operation technique of these bioabsorbable IM nails is very similar to that of metallic IM nails.

Preclinical Testing

Preclinical testing is not applied, as the materials have known toxicological profiles and well-established track record of safe clinical use in other application areas comparable to intramedullary nail fixation of forearm fractures. The manufacturing methods of bioabsorbable IM nails are well established in manufacturing of similar implants to different application areas.

Risk Analysis and Risk Assessment

The risk management of this clinical investigation has been made according to current risk management standard for medical devices (ISO 14971) and according to risk assessment the residual risk is acceptable. Based on risk assessment the risk is negligible that the 85/15 PLGA implants would cause any bioincompatibility reactions in this indication. The residual risk of each hazard was estimated based on the probability and severity of occurrence.

Objectives

Primary Objectives

The primary objective of the study is to evaluate the feasibility and efficacy of the new medical device in treatment of paediatric patients with forearm fractures. The key variables in this assessment are the evaluation of the functional and clinical outcome by measuring range of motion in forearm, wrist and elbow (e.g. measuring supination/protonation and flexion-extension movements), and subjective pain assessment during recovery. The primary objective will be met if these outcomes in the treatment group are at least comparable to those of the patients treated with standard of care (TEN nail), interpreted by using the Price's classification system (<15 degrees of change in motion range is excellent clinical outcomes), and Flynn's criteria for upper extremity assessment (<10 degress of change in motion range justifies satisfactory outcomes). The potential difference less than 10 degrees are to be determined not clinically significant. The raw results of clinical measurements and statistical significance of each finding are to be reported.

Secondary Objectives

The secondary objectives of the study are to evaluate the radiographic outcome of the forearm fracture treatment in patients treated using the study device. The key variables in assessment of these objectives are:

- fracture reduction and angulation,
- formation of bridging callus and consolidation (union, delayed union, non-union and malunion)

The method in assessment of key variables is plain radiographic evaluation. The secondary objective will be met if these outcomes in the treatment group are at least comparable to those of the patients treated with standard of care (TEN nail). According to the previous literature, angular deformity of <10 degrees in radius and/or ulna is to be determined not clinically significant [27-29].

Soft-tissue reaction against the biodegradable implant are to be studied by Magnetic Resonance Imaging (MRI) for a randomly selected sub-group of at least 10 patients.

Design of the Clinical Investigation

Type and Design of The Study

This is a randomized parallel-group ***two-centre*** study on the use of bioabsorbable intramedullary nail device for fixation of the radial and ulnar shaft fractures in children. All patients will receive the standard of care for other injuries caused by the trauma.

35 subjects will be enrolled at the University Hospital of Oulu and Central Hospital of Päijät-Häme to appreciate the potential drop-outs. The minimum number of patients in both groups (study implant vs. titanium implant) is 13. To minimize any selection bias, the patients will be sequentially randomized into these groups.

The study cannot be executed in a blinded fashion, because the orthopaedic surgeon and the operating room staff will inevitably be aware of the type of the implanted device. The patient must be also informed if the signed implant needs removal: the titanium alloy devices will be removed at 6 months, while the absorbable device will not require removal surgery.

Selection of the Study Population and Enrollment

The study begins with the signing and dating of the informed consent. All subjects and/or guardian must provide inform consent. During the consent procedure, the person obtaining consent must inform the subject of all elements of informed consent. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures, are performed until the subject has signed and dated the independent ethics committee approved informed consent form. Subjects must also meet the inclusion and exclusion criteria to be enrolled in the study. The participation in this clinical investigation is voluntary and the subject may interrupt the participation at any time, which is to be clearly informed.

1.1.1 Inclusion Criteria

- Subject's signed and dated informed consent
- Patients between 5 and 16 years of age, but diameter of bone marrow canal at least 2 mm
- Alert person oriented to place and time
- Acute, radius and/or ulna shaft fractures (antebrachium diaphysis)

- Satisfactory alignment must be in prior considered to be achieved by closed or open reduction

1.1.2 Exclusion Criteria

- Previous fracture or infection of the injured forearm bones (i.e. the radius and/or ulna)
- Severe overweight; body mass index (BMI) over 30
- Fracture older than ~~5~~ ***7*** days
- Distal fracture patterns in the transition zone of the distal metaphysis to diaphysis of the radius, classified as metaphyseal or metadiaphyseal fractures.
- Monteggia fracture dislocation
- Galeazzi fracture dislocation
- Open fracture other than a slight inside-out –wound and significant associated soft-tissue injury, particularly in connection with intra-articular fractures and polytrauma
- Pathological fractures with juvenile bone cysts
- Documented active infection at any anatomical site
- A known metabolic skeletal disease (such as osteoporosis or osteomalacia) or medication affecting the bone structure (cortisone treatment)
- Any underlying systemic illness (such as unbalanced diabetes mellitus or rheumatic disease) or condition which are known to affect resistance to infection
- Any other condition that in the judgment of the investigator would prohibit the subject from participating in the study or may hinder the collection of data and interpretation of the results.
- The patient has participated in any other device or drug related clinical trial within the previous month
- Patients certainly requiring open reduction to achieve satisfactory alignment

1.1.3 Number of Subjects

35 subjects will be treated under this protocol. At least 13 subjects are enrolled and treated in both groups to assess the safety and efficacy of the new implant. As there may occur

withdrawals there are more subjects to be treated than is required by samples size calculation.

Each study centre will operate at most two forearm fracture patients using the bioabsorbable intramedullary nails before the actual study subjects. This way the investigators will familiarize sufficiently with the surgical technique and use of bioabsorbable intramedullary nails in order that the outcome of the bioabsorbable intramedullary nails and titanium elastic nails would be comparable. These patients must be selected according to the chapter 9.2, and they and/or guardian must provide inform consent. The operations and the follow-up of their recovering will be performed according this clinical investigation plan; however, according to a decision of the study group, these patients will not be included in the evaluation of the outcome and key variables.

1.1.4 Screen Failures

Subjects who sign an informed consent form and fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the investigator is to maintain a screening log that documents the screening number, subject initials, and the reason for screen failure.

Prior Treatment

Prior to treatment the subjects will sign an informed consent form, stating that they are acquainted with the surgical procedure and study, and that they consent to participate in the study.

Reasonable efforts will be made to determine all relevant treatment received by the subject within 4 weeks prior to administration of the randomized treatment assignment. All relevant information will be recorded on the subject's CRF:

- Patient demographics
- Aetiology (e.g. bicycle accident, fall, sports) and injury mechanism
- Fracture type
    - proximal, middle, or distal shaft according to anatomic location
    - angular and rotational deformities, and displacement

Concomitant Treatment

1.1.5 Permitted Treatment

The following concomitant medications and therapies will be permitted:

- The treatment normally clinically applied when fixation is carried out using TEN nails is acceptable also in this study. In other words, the patients will receive all treatments needed for their injuries as the standard of care defines. The concomitant medications, therapies and treatments, which may reasonably be expected to interfere with the results of forearm fracture healing, will be reported in CRF.
- Due to the nature of the study, it is acceptable to leave out the detailed dosage information of concomitant medication in the CRF. This means that “N.A.” (= not applicable/available) can be documented into the Concomitant Medication CRF into the columns of “Single dose and unit” and “Frequency”.

1.1.6 Prohibited Treatment

- Subjects will not be permitted to use other investigational treatments during the 12 months following administration of the randomized treatment assignment.
- To avoid potential interactions that may interfere with fracture healing, the following concomitant medications and therapies are prohibited:
    - Osteoporosis medications (such as bisphosphonates and SERMs)
        - Hormone replacement and calcium-D-vitamin preparations are, however, permitted
- Additional procedures for the region of the study which may interfere fracture healing (such as ultrasound treatment)

Assessments and Procedures

1.1.7 Visit Schedule

For each subject, the study consists of assessments preoperatively, immediately after operation and the follow up visits postoperatively. The recommend time window of scheduled visits is ±7 days. The clinical assessments and procedures performed at each visit are shown in Table 2.

During these visits will be investigated: function of both arms, radiological fracture healing, well-being and incidence of complications.

Table 2 Assessment and procedures at each visit

Assessment	***Operation***		***4 week***	***12 weeks***	***26 weeks***	***52 weeks***	***104 weeks***
	Pre-operative	***Post-operative***					
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Call 6*	*Visit 7*
Informed consent, inclusion and exclusion criteria	X						
Demographics, medical history	X						
Injuries and comorbidities	X						
Randomization	X						
Fracture reduction and fixation	X						
Cast removal			X				
TEN nail removal					X		
Primary performance variable	***Operation***		***4 week***	***12 weeks***	***26 weeks***	***52 weeks***	***104 weeks***
	Pre-operative	***Post-operative***					
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Call 6*	*Visit 7*
Functional and clinical outcome evaluated by measuring rate of motion			X	X	X		X
Pain assessment		X	X	X	X	X	X
Subjective		X	X	X	X	X	X

result							
Secondary variables	***Operation***		***4 week***	***12 weeks***	***26 weeks***	***52 weeks***	***104 weeks***
	Pre-operative	***Post-operative***					
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Call 6*	*Visit 7*
Radiographic outcome and bone union formation evaluated by plain radiographs	X	X	X	X	X		X
Radiographic outcome and bone union formation evaluated by MRI imaging		X*		X*		X*	X*
Safety and tolerability variables	***Operation***		***4 week***	***12 weeks***	***26 weeks***	***52 weeks***	***104 weeks***
	Pre-operative	***Post-operative***					
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Call 6*	*Visit 7*
Adverse events	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Conclusion of participation							X

* Radiographic outcome and bone union formation of 5-10 subjects will be evaluated by MRI imaging immediately after operation and three follow up visits

1.1.8 Surgical Procedure

The surgery will be performed by a paediatric surgeon, paediatric orthopaedic surgeon, orthopaedic surgeon or by a resident specializing in paediatric orthopaedic surgery. In surgery, standard AO techniques will be applied. The surgery will have the following steps:

1. Patients are placed supine on a standard operating room table and general anesthesia is induced.
2. The arm is prepared and draped in the usual sterile fashion. A tourniquet is used as necessary, according to the decision of the operating surgeon.

3. Following necessary irrigation of any open wounds, attention is then turned to IM nailing.
    a. The more angulated/displaced bone is addressed first and stabilized.
    b. If the second bone reduces anatomically with stabilization of the first bone, it is treated closed
4. Either a bone awl or a 4.5-mm drill bit is used to make an entry portal into the cortical bone
    a. To treat the radius, a 1-cm longitudinal incision is made over the dorsolateral metaphyseal surface just proximal to distal physis (C-arm image is used to aid in the placement of the incision), with care taken to avoid the dorsal branch of the superficial radial nerve.
    b. All ulnae are treated by inserting the IM device from proximal to distal, avoiding the proximal physis using the above technique.
5. If an acceptable reduction cannot be achieved closed, then a mini open incision directly over the fracture site is made and any interposing tissue removed.
6. Bone marrow canal is reamed using the metallic intramedullary nail (Ø 2.0, 2.5, 3.0 or 3.5 mm).
    a. The reaming metallic intramedullary nails are left to bone marrow canals until it is time to insert bioabsorbable IM nail. The metallic intramedullary nails are removed and replaced by bioabsorbable IM nail one by one.
    b. The diameter of the metallic intramedullary nail and bioabsorbable IM nail will be determined according to the estimation about the diameter of bone marrow canal by radiograph. The largest possible implant is to be applied.
7. After reaming of canal, the bioabsorbable IM nail (Ø 2.0, 2.7 or 3.2 mm) is inserted to canal using nail inserter.
    a. In the installation of bioabsorbable IM nail the “slide hammer” of the insertion tool has to be used without rotational motion, because the nail may expand because of heat due to rotational motion and friction.
    b. Use of drill sleeve is recommended during installation of the nail.
8. Following insertion of the bioabsorbable IM nail, it is cut using oscillating saw or hot wire.
9. The wounds are closed in layers using standard principles.
10. The immobilization of forearm is performed by dorsal plaster cast with volar support for 4 - 6 weeks with the elbow flexed to 90 degrees. After that, additional appropriate immobilization should be considered by the treating physician.
11. Sport activities should be limited for 3-6 months.

The operation technique is much the same as that with metallic IM nailing fixation. The differences of techniques are that

- the separate reaming of bone marrow is not performed with metallic IM nail fixation
- the end of the TEN nail is left out about 6 - 7 mm from the cortex for removing of the nail
    - Wound is closed in layers over the end of the TEN nail
- the TEN nail is removed in second operation after 6 months in general anesthesia.

1.1.9 Functional and Clinical Outcome Measurements

Healing of the injury will be clinically monitored using repeated functional measurements, pain assessments and by means of standardized questionnaires. The follow-up will be performed according to table 2. The functional examinations will include the supination and pronation of the forearm, flexion and extension of elbow, dorsiflexion and palmar flexion of the wrist using a goniometer, and their comparison to the corresponding measurements of the subject's healthy forearm.

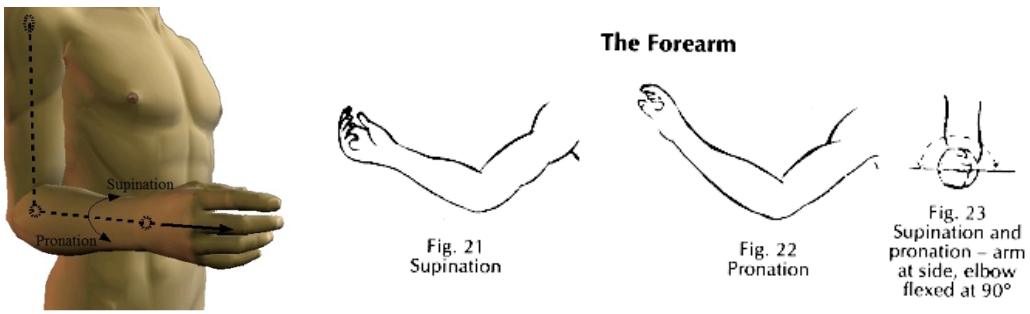

Figure 1 Determination of forearm's pronation and supination angles

In measuring of pronation, the vertical limb of the goniometer is placed parallel to the long axis of the humerus, while the horizontal limb is placed on the back of the wrist (to eliminate additional motion at the radiocarpal joint). In the measuring supination the horizontal limb is placed on the anterior aspect. The average range of protonation/supination is 90/90 degrees (50/50 degrees necessary for activities of daily living). ***Flynn's criteria for elbow assessment is used to evaluate the clinical significance of outcomes (excellent and good comprising satisfactory, and fair and poor comprising unsatisfactory), as well as the classification by Price.***

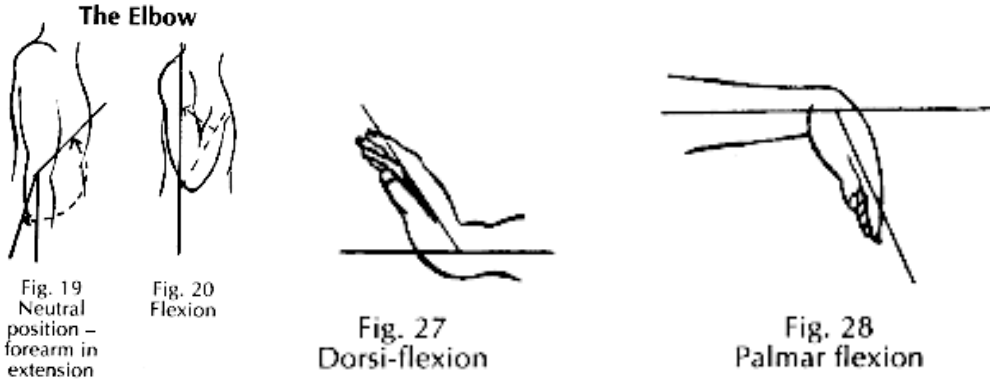

Figure 2 Determination of A) elbow's flexion and extension, B) wrist's dorsiflexion and palmar flexion

Clinical outcome and fracture union will be also assessed by the absence of pain and bony tenderness at fracture site. The subjects will be also asked to perform self-assessment of perceived pain in the region of study using 10 cm visual analogue scale (VAS) as a measure of pain severity.

1.1.10 Radiographic Evaluations

This study will involve normal repeated radiographic examinations of the forearm for assessment of outcome, progress of fracture union and also possible development of complications related to injury or treatment.

Plain Radiographs

The plain radiographs in standard anteroposterior (AP) and lateral projections will be taken before and after surgery, followed by repeated radiographs according to table 2.

The parameters defined from forearm's plain radiographs are

- fracture reduction and retention
- fracture angulation
- fracture union as bridging callus by the presence of obliteration of fracture lines (union, delayed union, non-union)
- increased/decreased radial bow (fracture malunion)
- limb-length discrepancy
- complications related to injury or treatment (implant-related osteolysis)

The angulation of the fractures will be measured on anteroposterior and lateral radiographic views. Radiographic union will be defined as the presence of bridging callus at all visualized cortices on the anteroposterior and lateral radiographic views. Delayed union will be classified as incomplete healing at 10 weeks in children <9 years of age and at 12 weeks in children ≥9 years of age. [23]

At latest follow-up malunion will be quantified by measurement of the amount and location of the maximum radial bow in relation to the contralateral, normal forearm as described by Schemitsch and Richards. The radial bow will be measured on the anteroposterior radiograph of the forearm, which includes the wrist and elbow joints.

Limb-length discrepancy will be assessed by measurement of the distances between lateral epicondyle of the humerus and radial styloid process in both limbs.

MR Imaging

The parameters defined from forearm's MR images are

- fracture reduction and retention
- fracture angulation
- fracture union as bridging callus by the presence of obliteration of fracture lines (union, delayed union, non-union)
- fracture malunion (radial bow, Limb-length discrepancy)
- complications related to injury or treatment (implant related osteolysis and detection of IM nail failure)
- soft-tissue reactions (oedema, abnormal fibrotic tissue, post-traumatic calcification) in the surroundings
- bioabsorption of the investigational device

Evaluation of Variables

The following variables will be measured from each subject at designed visits in evaluation of the efficacy and safety of fixation. The radiographic measurements are performed by an experienced paediatric radiologist, familiar with children's trauma.

1.1.11 Primary Performance Variable

Evaluation of functional and clinical outcome consists of following determinations:

- Measurements of the range of motion (ROM) in the forearm, expressed as degrees ± SD
    - Loss of supination and pronation of the forearm (graded according to the table below),
    - Loss of flexion and extension of elbow and
    - Loss of dorsiflexion and palmar flexion of the wrist, graded according to the Flynn's criteria (<10 degrees of chance are excellent or good i.e. satisfactory; >10 degrees of chance are fair or poor i.e. unsatisfactory); and Price's classification.
- General pain and pain at fracture site assessed by VAS, expressed as mm ± SD
    - Duration of post-operative medication for pain

Table 1 Classification of outcome, graded using a system described by Price [25]

Outcome	Loss of Forearm Rotation and Symptoms
Excellent	≤15° loss of forearm rotation and no complaints with strenuous activity
Good	A loss of forearm rotation of 15° to 30° and only mild complaints with strenuous physical activity
Fair	A loss of forearm rotation of 30° to 90° and mild complaints during activities of daily living
Poor	All other outcomes

1.1.12 Secondary Variables

Forearm's plain radiographs in AP and lateral projections and MRI imaging will be used to determine:

- Fracture reduction and retention
- Fracture angulation, expressed as degrees ± SD (graded according to Table below)
- Bony union formation and rate (union, delayed union, non-union, malunion)

1.1.13 Safety Variables

Incidence of adverse events (AE) and serious adverse event (SAE) will be expressed as proportion per group. These consist of e.g. complications related to injury or treatment and will be separated into resolved versus long-term or non-resolved complications, which included a need for return to the operating room. Monitored AE's are:

- Fracture delayed union, nonunion and malunion
- Incidence of infection
- Intra-operative complications related to fixation hardware
- Need for secondary reduction due to fracture instability
- Osteolysis
- Bioincompatibility reactions
- Mechanical implant failure

The potential drop-outs by any reason are recognized and reported, despite the lack of 2-year follow-up data, whilst no comparisons at end-point are available.

1.1.14 Other Variables

Other variables documented in CRF are:

- Operation time
- Number of days lost from usual activities
    - Parents lost working days
- Length of hospitalization stay
- Complaints in daily living
- Esthetics

Statistics

Recommended statistical methods will be applied. All deviations made after approval of the CIP will be described and justified in the final study report.

Sample Size Considerations

Primary outcome variable in this study is loss of supination and pronation within 6, 12, 26, 52, and 104 weeks after surgery. The non-inferiority margin is set to be 80 % in the calculations (=Power).

It is previously known that the forearm pronation in this age group is 81.2 degrees (95% CI 79.6-82.28) and 79.6 degrees (95% CI 78.8-80.4) in girls and boys, respectively. The corresponding supination archs are 90.0 degrees (95% CI 88.0-92.0) and 87.8 degrees (95% CI 85.7-89.9). [26] The standard deviation (SD) is 6.1 degrees in pronation and 7.6 degrees in supination. We determined that the new method (ActivaNail –intramedullary fixation) should

result to the forearm rotational range of motion that is not more than 15 degrees lower, compared to the rotational range of motion in TEN group, according to the Price's classification (<15 degrees of decrease refers to excellent outcome).

Difference between means in the groups is set as 7.0 and the Alpha as 0.05. The sample size is estimated to be 13 experimental subjects and 13 controls according to an unpaired two sample Student t test. This study population will also be exclusively large enough to recognize decrease in the ROM that is clinically significant (>15 degrees of decrease in supination or pronation in ActivaNail compared to TEN group).

Statistical Hypothesis

The following hypothesis will be tested for the primary efficacy variable:

H_0: Investigational device is inferior to comparative devices

H_1: Investigational device is non-inferior to comparative devices

The non-inferiority limit is set to 80 %. Thus, non-inferiority is shown if the upper limit of the 95% confidence interval for the difference is less than or equal to 5 %.

Statistical Methods

All operated subjects who reach the 2-year follow-up will be included in the statistical analysis. Study data will be tabulated by treatment groups with descriptive summary statistics.

The conventional level of 5% will be considered the level of statistical significance. All tests will be two-sided. Accordingly, 95% confidence intervals will be used.

Normality assumptions will be checked using normal probability plot for residuals. The use of transformation for a particular variable will be decided after examining the assumptions with the original scale of measurement. Analysis may be repeated without possible outliers.

The primary variable will be analyzed using an analysis of variance model for repeated measurements. Treatment differences with 95% confidence intervals will be calculated from the model. If the assumptions for the parametric models are not met suitable non-parametric models will be used.

Adverse Events

The safety variables to be evaluated include adverse events (AE), findings from physical and radiographic examinations, subjective reports of pain and functional outcome assessments. Further, all drop-outs will be reported. The adverse event data will include the following displays:

- AEs categorized by body system
- AEs categorized by severity grades 1-4 (mild, moderate, severe, life-threatening)
- AEs involving the region under study (RUS) specifically:
    - Fracture delayed union, nonunion and malunion
    - Hardware failure
    - Infection

All Serious Adverse Events (SAE) will be reported within 24 hours to the Sponsor. The SAEs include death, life-threatening event, medically important event, device malfunction, hospitalization, accidental exposure, persistent disability or incapacity, and cancer. In emergency SAE cases, the patients are requested to seek help in the Emergency room of the University Central Hospital. Any adverse events and their effects are reported using Case Report Form (CRF).

Quality Management

Monitoring Arrangements

The sponsor is responsible for the monitoring of this study. The principal investigator will provide sponsor with the data recorded during the study without personal identification data to allow the sponsor to check the compliance of the study with the CIP. The sponsor will appoint a monitor for assessing the investigator's compliance with the Clinical Investigation Plan and for performing source-data verification. A monitoring plan and report will be prepared.

Data Management

The study data of the CRFs will be stored at the research sites and copies without personal identification data will be sent to the sponsor for storing.

Quality Assurance

Bioretec has a certified Quality Management System according to ISO 13485:2003. Investigational devices will be tested according to SOP's of the Bioretec Ltd using the test equipment maintained and calibrated according to relevant SOP's of Bioretec Ltd.

Discontinuation and Withdrawal of Subjects

A subject may be discontinued (withdrawn) from the study at any time if the subject or the investigator believes it is not in the best interest of the subject to continue participation in the study. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal. All study data provided up to the time of withdrawal will be collected and reported. This information will be recorded in the subject's source documentation and in the CRF. Subjects who discontinue their participation or are withdrawn from the trial will be asked to participate in a final study visit at 104-week follow-up visit.

Termination of the Study

The sponsor may terminate individual subject or group of subjects, or the entire investigation, at any time for any of the following reasons:

- Failure to enrol subjects
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the test device
- Suspected lack of efficacy of the test device
- Administrative decision.

If the investigator terminates the study prematurely, the investigator provides the ethical committee and the sponsor with a written statement describing why the study was terminated prematurely. Prompt compliance with this requirement is essential so that the sponsor may comply with its regulatory obligations.

CIP Amendments and Deviations

All amendments to the CIP with the justifications will be agreed and recorded between sponsor and the principal investigator. Any deviation to this clinical investigation plan made by investigators shall be recorded with an explanation for deviation and reported to sponsor. The significance of deviation will be determined by sponsor. When appropriate, Ethical Committee and other appropriate regulatory bodies are informed.

Publication Policy

If on completion of the study the data warrants publication, the investigator may publish the results in recognized (refereed) scientific journals. The investigator shall submit reports, abstracts, or manuscripts to the sponsor for review prior submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including without limitation, the deletion of confidential information. The principal investigator shall act in good faith upon requested revisions. The principal investigator shall delay submission of such publication or presentation materials for up to 90 days in order to have a patent application(s) filed.

Subject Injury

In general, if a subject is injured as direct result of the test device, the sponsor will pay for the reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the subject's medical insurance, a government program, or other responsible third party.

Report Forms

Case report forms (CRF) are records of data of each subject as defined by the CIP. Data to be collected in this study will be entered on CRFs. All data recorded is recommended to be verifiable in hospital or patient records. The CRFs are required for each study subject. The investigator should confirm the content CRF by signing and dating the applicable pages. Original completed forms will be maintained by the principal investigator. A copy of each CRF without personal identification will be sent to sponsor.

References

1. Koval K.J. and Zuckerman J.D., *Handbook of Fractures*, 3rd ed. [2006], p. 540.
2. *Campbell's Operative Orthopaedics*, 10th ed., [2003], vol 2, p. 1405.
3. Noonan K.I. and Price C.T., *J. Am. Acad. Orthop. Surg*., 6 [1998] 146.
4. Widjaja A.B., Eng K. and Griffiths J., *ANZ J.Surg.,* 77 [2007] 873.
5. Smith V., Goodman H.J. Strongwater A. and Smith B., *J. Pediatr. Otrhop.,* 25 [2005] 309.
6. Luhmann S.J., Schootman M., Schoenecker P.L., Dobbs M.B. and Gordon J.E., *J. Pediatr. Orthop.*, 24 [2004] 1.
7. Celebi L., Muratli H.H., Dogan O., Yagmurlu M.F., Aksahin E., Bicimoglu A., *Acta Orthop. Traumatol. Turc.,* 41 [2007] 175.
8. Carmichael K.D. and English C., *Orthopedics,* 30 [2007] 379.
9. Kapoor V., Theruvil B., Edwards S.E., Taylor G.R., Clarke N.M.P. and Uglow M.G., *Injury, Int. J. Care Injured,* 36 [2005] 1221.
10. Kose O., Deniz G., Yanik S., Gungor M. and Islam N.C., *Journal of Othropaedic Surgery,* 16 [2008] 165.
11. Altay M., Aktekin C.N., Ozkurt B., Birinci., Ozturk A.M. and Tabak Y., *Injury, Int. J. Care Injured,* 37 [2006] 966.
12. Bombaci H., Guneri B., Caboglu F. and Gorgec M., *Orthopaedics*, 30 [2007] 866.
13. Waseem M. And Paton R.W., *Injury, Int. J. Care Injured,* 30 [1999] 21.
14. Hughes T.B., *Clin. Orthop*., 445 [2006] 169.
15. Waris E., Konttinen Y.T., Ashammakhi N., *Expert. Rev. Med. Devices,* 1 [2004] 229.
16. Bostman O., Mäkela E.A., Törmälä P., and Rokkanen P., *J. Bone Joint Surg. (Br).,* 71 [1989] 701
17. Hope P.G., Williamson D.M., Coates C.J. and Cole W.G*., J. Bone Joint Surg. (Br).* 73 [1991] 965.
18. Partio E.S., Merikanto J., Heikkila J.T., *J. Paediatr. Orthop.,* 12 [1992] 646.
19. Gortzak Y., Mercado E., Atar D. and Weisel Y., *J. Pediatr. Orthop.,* 26 [2006] 3942.
20. Lautiainen I., Merikanto J., Södergård J., Rokkanen P., Törmälä P., Mäkelä E.A., Scandinavian-Hungarian Hand Society Meeting 2000, Kuopio, Finland, "Bioabsorbable Intramedullary Fixation in Children's Forearm Fractures", p. 19
21. Mäkelä E.A., Böstman O., Merikanto J., Södergård J., Törmälä P., Rokkanen P., XXX11 World Congress of the International College of Surgeons, October 8-12, Year 2000, Singapore, " Bioabsorbable Fracture Fixation in Children", R24, p. 24

22. Mäkelä E.A., Lautiainen I., Merikanto J., Södergård J., Rokkanen P. Törmälä P., Valtakunnalliset Lääkäripäivät, Helsingin Messukeskus 6-10.1.2003, ”Intramedullary Bioabsorbable Nail Fixation of Forearm Fractures in Children”, B18, p. 295
23. Greenbaum B, Zionts LE, Ebramzadeh E. Open fractures of the forearm in children. J Orthop Trauma. 2001;15:111–118.
24. Schemitsch EH, Richards RR. The effect of malunion on functional outcome after plate fixation of fractures of both bones of the forearm in adults. J Bone Joint Surg Am 1992;74(7):1068–78
25. Price CT, Scott DS, Kurzner ME, et al. Malunited forearm fractures in children. J Pediatr Orthop. 1990;10:705–712.
26. Soucie JM, Wang D et al. Range of motion measurements: reference values and a database for comparison studies. Haemophilia. 2011; 5: 500-507
27. Price CT, Knapp R. Osteotomy for malunited forearm shaft fractures in children. Journal of Pediatric Orthopedics, 2006, 26.2: 193-196
28. Matthews L, Kaufer H, Garver D, Sonstegard D. The effect on supination-pronation of angular malalignment of fractures of both bones of the forearm. J Bone Joint Surg Am 1982; 64(1): 14-17
29. Tarr R, Garfinkel A, Sarmiento A. The effects of angular and rotational deformities of both bones of the forearm. An in vitro study. J Bone Joint Surg Am 1984; 66(1): 65-70

Appendixes

1. Information Brochure given to trial subject (in Finnish)
2. Informed Consent Form (in Finnish)
3. A228-CRF-1 Case Report Form

Appendix 1: Information Brochure given to trial subject (translated in English)

Oulu University Hospital, department of pediatric orthopaedics and traumatology

Dear attendee,

We have offered you the possibility to attend the study about operative treatment of pediatric forearm fractures. The study patients are not in danger of health risks.

The study aims to compare the new technique in treating of pediatric forearm fractures with traditional technique. In the new technique, the implants are made of biodegradable material whereas the traditional implants are made of titanium. The benefit of biodegradable material is that it absorbs via physiological pathways so the implant removal surgery is therefore not needed.

This study is the first of its kind conducted in Finland. Because of this the participation is very valuable for us. The research gives us knowledge that helps patient treatment in the future.

The principal clinical investigator is Juhani Merikanto Adjunct Professor, Ph.D. orthopaedic and traumatology. Coordinating Investigator is Jaakko Sinikumpu, Adjunct prof. Ph.D. pediatric orthopaedics and traumatology, Oulu University Hospital.

Taking part in the research is entirely voluntary. After the primary surgery, there will be six follow-up visits in the out-patient clinic of Oulu University Hospital during the next two years. Your doctor will gladly answer any of your questions regarding of the study. The written letter of consent is given to you prior the study.

All the medical information and responses will be kept strictly confidential. The data collected in unidentifiable. The study plan was approved by Hospital Ethics Committee of Tampere Hospital District, Tampere, Finland.

In Oulu

Willy Serlo	Juha-Jaakko Sinikumpu
Professor, Ph.D.	adjunct prof. Ph.D. pediatric orthopaedic and
Pediatric surgeon	traumatology

Appendix 2: Informed Consent Form (translated in English)

BIOABSORBABLE INTRAMEDULLARY NAIL FIXATION OF FOREARM FRACTURES IN CHILDREN

Contact Information

Sponsor:

Bioretec Ltd.
Hermiankatu 22, P.O. Box 135, FI-33721 Tampere, FINLAND Primary contact: Minna Veiranto, Director, Clinical Affairs
Tel: +358 40510 3681, E-mail: minna.veiranto@bioretec.com

Principal Clinical Investigator:

Juhani Merikanto, Adjunct prof., Ph.D., Pediatric surgeon, orthopaedics and traumatology, Näsilinnankatu 35 B 22, 33200 TRE, tel: 044-0200226, fax 03-31164346, juhani.merikanto@pshp.fi

Coordinating Investigator:

Jaakko Sinikumpu, Adjunct prof., Ph.D., Pediatric surgeon, orthopaedics and traumatology, tel: 08 3152011, juha-jaakko.sinikumpu@ppshp.fi

Institutions, in which the clinical investigation will be conducted, and investigators:

Oulu University Hospital, Oulu, Finland, Department of Paediatrics, Surgery and Orthopaedics
P.o. Box 23, FIN-90029, OYS, Oulu, FINLAND

Päijät-Häme Central Hospital, Department of Surgery, Unit of Paediatric Surgery, Keskussairaalankatu 7, FIN-15850, Lahti, FINLAND

-Antti Kyrö, M.D., Ph.D., Orthopaedic surgeon

THE LETTER OF CONSENT

THE NAME OF THE STUDY: Operative treatment of forearm shaft fractures in children and Adolescents

THE STUDY ORGANIZATION: Oulu University Hospital, Oulu, Finland/
Päijät-Häme Central Hospital, Lahti, Finland

MAIN INVESTIGATORS:
Juha-Jaakko Sinikumpu, Ph.D., adjunct professor, pediatric orthopaedics and traumatology, pediatric surgeon
Linda Korhonen, M.B., Ph.D. candidate
Juhani Merikanto, Ph.D., adjunct professor, orthopaedic surgery, pediatric surgeon

I have been given written letter of consent. I give my approval that my medical information is used in this study.
I understand that the participation is voluntary. I have the right to interrupt the participation at any time of the study.
I also understand that my medical information and responses will be kept strictly confidential. I give permission for members of the research team to have access to my responses.
I agree for the data collected from me to be used in future medical research.
I agree to participate the research.

Place _____

Date _____/_____ 200__

_____
Signature of the attendee

_____
Name

_____
Date of birth

_____