A pre-market, single group First in Human (FIH) study to evaluate the safety and performance of a Class III medical device (OsStic Implant) to treat Tibial Fractures.

CLINICAL INVESTIGATIONAL SYNOPSIS

Title:	Safety and Performance of OsStic Synthetic Injectable Structural Bio Adhesive Bone Void Filler in a First in Human Application to treat Tibial Fractures.
IRAS Project ID:	360651
Version and Date:	Version 01
Principal Investigator:	Prof. Peter Giannoudis, MD, FACS, FRCS University of Leeds
Sponsor:	Biomimetic Innovations Ltd 4D Western Business Park, Shannon, Co. Clare, Ireland

This clinical study will be conducted in accordance with Current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonization), ISO 14155, Clinical Investigation of medical devices for Human Subjects Guidelines and EU Directives.

CONFIDENTIAL

The information contained in this document is proprietary and private and will not be disclosed to others than the Investigator(s) and his/her/their staff, applicable IRB(s)/EC(s) and regulatory authorities without prior written approval except to the extent necessary to obtain informed consent from those persons to whom the medication may be administered.

1.0 Study Synopsis

Study Title	A pre-market, single group First in Human (FIH) study to evaluate the safety and performance of a Class III medical device (OsStic Implant) to treat Tibial Fractures.
Study Short Title	OsStic BVF First in Human Clinical Study
IRAS Project ID	360651
Study Sponsor	Biomimetic Innovations Ltd 4D Western Business Park, Shannon, Co. Clare, Ireland
Clinical Phase	Pre-market clinical investigation of a Class III Investigational Medical Device.
Study Design	Single group First-in-Human (FIH) clinical investigation evaluating the safety and performance of the OsStic Synthetic Injectable Structural Bio-Adhesive Bone Void Filler (BVF) will be conducted in a single centre (Leeds General Infirmary University Hospital). The target population will comprise of Adult Patients, presenting with traumatic, closed, depression fracture of the proximal tibia (limited to AO fracture classification B2 & B3), aged between 18-80 years, of any biological sex. An initial safety cohort of five (5) patients will be enrolled. Following completion of their 3-month (Day 84) follow-up, an interim analysis will be conducted and reviewed by an independent Data Safety Monitoring Board (DSMB). Progression to full enrolment (up to 15 patients) will depend on DSMB recommendations based on observed safety and device performance. Each patient will undergo surgery involving OsStic implantation, followed by a structured follow-up through 12 months (Day 365). Scheduled assessments will occur on Days 7, 14, 28, 42, 84, 182, and 365, with allowed visit windows. These visits include X-ray and CT imaging, safety evaluations, wound assessments, pain scoring (Numeric Pain Rating Scale), Pain on weight bearing: FIX-IT Measure and patient-reported outcomes (SF-12v2™, EQ-5D™). Load, gait, and balance will also be evaluated using XSENSOR insoles. The DSMB will review safety data periodically and assess all Serious Adverse Events (SAEs) as they occur. An adaptive interim analysis is planned once at least five patients complete the 3-month (Day 84) (Visit 7), guiding continuation or study modification based on predefined safety endpoints.
Investigational Medical Device	OsStic Synthetic Injectable Structural Bio Adhesive Bone Void Filler.
Investigational Medical Device Short Name	OsStic BVF
Investigational Medical Device Intended Use	OsStic BVF is a structural, mechanically enhanced bio-adhesive for reduction, provisional fixation, and void filling of Peri-articular fractures or defects to enhance structural stability where standard fixation alone cannot provide sufficient support for functional mobility.

Investigational Medical Device Description	OsStic Synthetic Injectable Structural Bio Adhesive Bone Void Filler (hereafter referred to as OsStic BVF) is an injectable, moldable and fast-setting synthetic bone graft. OsStic BVF self-cures in situ within a bone void or fracture site to provide a bone graft that can support provisional fixation (e.g., K-Wires, plates, screws) to assist and support bone fragments during the surgical procedure. The final cured OsStic BVF graft provides support intra-operatively, performs load sharing with adjunct hardware to facilitate fracture healing. OsStic BVF resorbs and is replaced by the growth of new bone during the healing process. The resultant structure, chemistry and micro-porosity of OsStic BVF makes it an effective osteoconductive and osteo-integrative biomaterial implant, with excellent biocompatibility and mechanical properties. OsStic BVF was specifically formulated to set in a wet field environment and exhibits beneficial handling characteristics. The curing reaction that occurs as OsStic BVF hardens is not exothermic and therefore does not result in any thermal damage to the local tissues. The product is presented as a kit; containing after mixing 10cm³ of graft material.
Clinical Investigation Rationale	Tibial plateau fractures (TPFs) account for approximately 1.3% of all fractures, occurring as a result of high-energy injuries in younger patients and as secondary injuries to low-energy trauma in the elderly. These injuries can induce major damage to the structure and function of the knee joint and may lead to long-term pain and functional impairment. Moreover, due to the risk of cartilage degeneration, patients may develop osteoarthritis, requiring total knee replacement. Consequently, TPF can impose a significant burden on patients, the health care system, and society as a whole. Although the trend in management of tibial plateau fractures has been toward early mobility, the period of immobilization that can be safely tolerated remains uncertain. Some studies demonstrate that consensus regarding weight-bearing aftercare for tibial plateau fractures is limited. A large majority of surgeons do not strictly follow the AO guideline or their own local protocol. This study will evaluate the safety in a first in human study using OsStic BVF (a cohesive synthetic injectable bone void filler comprising of alpha-tricalcium phosphate (α-TCP), tricalcium silicate, dicalcium silicate and phosphoserine. The addition of phosphoserine is solely to improve physical and mechanical properties and not intended for Osteoinduction and Osteogenesis.
Study Aim	The aim of the study is to investigate safety and performance of OsStic BVF in conjunction with DePuy Synthes LCP Proximal Tibial Plating System for the repair of tibial plateau fractures.
Study Objectives	The Study Objectives are: To assess the safety of OsStic BVF on pain, functional outcomes in terms of weight-bearing, and overall patient satisfaction.
Implant of the Medical Device	OsStic BVF Implant is applied to patients presenting with traumatic, closed, depression fracture of the proximal tibia (AO: 41 B2 or Schatzker Type III Fractures) and split depression fractures (AO: 41 B3 or Schatzker Type II Fractures).
Study Population	Adult Patients, presenting with closed tibial plateau fracture, aged 18-80, Skeletally mature, of any biological sex.
Sample Size	The Sample Size will be 15 Patients
Inclusion Criteria	1. Patients with traumatic, closed, depression fracture of the tibial plateau (proximal tibia) (limited to AO fracture classification B2 & B3).

	2. Candidate patient for bone grafting. 3. Being ambulatory before the injury. 4. Written informed consent. 5. Patients with communicative ability to understand the procedure and participate in the study and comply with the follow up program. 6. Willing and able (in the opinion of the study team) to provide informed consent and participate in all study activities and visits schedule.
Exclusion Criteria	1. Open /compound tibial plateau fracture. 2. AO fracture classification Type C. 3. Pathological (Metastatic Tibial Fracture). 4. Multi-segmental nature of this fracture (more than one fracture site within tibia for intervention). 5. Polytrauma (defined as injury severity score of 17 or more). 6. Active systemic infection. 7. Clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation. 8. Exposure to drugs that can affect the bone metabolic state within the past three months. 9. Any pre-existing calcium metabolism disorder (e.g., hypercalcemia). 10. Irreversible coagulopathy or bleeding disorder. 11. Receiving chemotherapy, radiation treatment or immunosuppression drugs. Patients on long term opioid medication buprenorphine, diamorphine, fentanyl, morphine and oxycodone. 12. History of physical or psychological condition that contraindicates the use of an investigational device or render the patient at high risk from treatment. 13. Pre-existing osteoarthritis. 14. Currently enrolled in any other study which may impact on the results of the present study. 15. If female: pregnant, breastfeeding, or not currently using and not willing to use an effective form of contraception for 12 months post-surgery.
Concomitant Medications Not Allowed	Immunosuppressive agents, e.g., systemic administration of methotrexate, azathioprine, thalidomide for autoimmune diseases or cancer. Systemic corticosteroids. Anti-coagulants. Non-steroidal anti-inflammatories. Drugs to treat Infection. Short-term and Long-term opioid medication.
Duration and follow up of the clinical investigation	12 Months Evaluation and 6 Months for final reporting Total 18 Months

Study Flow Chart	Visit	Procedures	Day
	Visit 1 (V1 – Screening)	• Informed Consent collection (24 hours for the patient to decide). • Eligibility criteria evaluation Demographics / Medical history. • CT scan of the knee. • AP & LAT x-rays of the knee.	D -7
	Visit 2 (V2 – Surgery)	• Device implantation: application of OsStic BVF implant at surgical site. • Evaluation of Technical Success. • Ease of Use questionnaire. • Vital signs. • Concomitant Medications. • Adverse Events. • Fluoroscopic Images.	D 0
	Visit 3 (V3 – Control 1)	• AP & LAT x-rays of the knee. • CT scan of the knee for safety and baseline data for evaluation of OsStic resorption. • Load, Gait and Balance (std protocol) using XSENSOR insoles • Adverse events/ safety assessment variables/ Wound checks. • Numeric Pain Rating Scale for pain • SF-12v2™ + EQ-5D™ • Pain relief medications questionnaire review.	D 7 +/-3 (1W)
	Visit 4 (V4 – Control 2)	• Load, Gait and Balance (std protocol) using XSENSOR insoles. • Numeric Pain Rating Scale for pain. • Pain relief medications, questionnaire review.	D 14 +/-3 (2W)
	Visit 5 (V5 – Control 3)	• Load, Gait and Balance (std protocol) using XSENSOR insoles. • Numeric Pain Rating Scale for pain • Pain relief medications, questionnaire review.	D 28 +/-3 (4W)
	Visit 6 (V6 – Control 4)	• AP & LAT x-rays of the knee. • CT scan of the knee for safety and evaluation of OsStic resorption. • Load, Gait and Balance (std protocol) using XSENSOR insoles. • Adverse events/ safety assessment variables/ Wound checks.	D 42 +/-3 (6W)

		• Pain on weight bearing: FIX-IT Measure. • Numeric Pain Rating Scale for pain • SF-12v2™ + EQ-5D ™ • Pain relief medications questionnaire review.	
	Visit 7 (V7-Control 5)	• AP & LAT x-rays of the knee. • Load, Gait and Balance (std protocol) using XSENSOR insoles. • Adverse events/ safety assessment variables/ Wound checks. • Pain on weight bearing: FIX-IT Measure. • Numeric Pain Rating Scale for pain • SF-12v2™ + EQ-5D ™ • Pain relief medications questionnaire review.	D 84 +/-7 (12 W)
	Visit 8 (V8- Control 6)	• AP & LAT x-rays of the knee. • Adverse events/ safety assessment variables/ Wound checks. • Pain on weight bearing: FIX-IT Measure. • Numeric Pain Rating Scale for pain • SF-12v2™ + EQ-5D ™ • Pain relief medications questionnaire review.	D 182 +/-14 (26 W)
	Visit 9 (V9- Control 7)	• AP & LAT x-rays of the knee. • CT scan of the knee for safety and evaluate OsStic resorption. • Adverse events/ safety assessment variables/ Wound checks. • Numeric Pain Rating Scale for pain • SF-12v2™ + EQ-5D ™ • Pain relief medications questionnaire review.	D 365 +/-28 (52 W)
Study Outcomes	**<u>Primary Outcomes:</u>** Safety profile of OsStic BVF in tibial fracture surgery. Occurrence of adverse events, device complaints and device-related incidents (duration of study Day 365 (52 W)). The study will be monitored by an independent Data Safety Monitoring Board (DSMB). **<u>Secondary Outcomes:</u>** 1. Trend of global pain scores over duration of study to Day 365 (52 W). 2. Radiological assessment of bone healing [26 weeks]		

	3. Rasmussen Radiological Score. 4. Numeric Pain Rating Scale for pain while weight bearing: FIX-IT Measure (26 W). 5. Load, gait and balance XSENSOR monitoring (Time course Day 0 – Day 84 (12 W)). 6. SF-12V2™ (12-item Short Form Health Survey (SF-12); and EQ-5D™ over duration of study to Day 365 (52 W). **Safety Endpoints** 1. Peri-operative complications 2. Evaluation of any loss of fracture alignment, reduction, and development of non-union.
Study Endpoints	1. Number of patients recruited during study period. 2. Proportion of participants for whom data is available for each outcome measure at each time-point. 3. Rasmussen radiological score. 4. Proportion of patients healed by Day 84 (12W) 5. Incidence of surgical re-intervention Day 182 (26 W) post primary surgery. 6. Patient-reported outcomes (pain and function) at discharge and follow up at Day 7 (1W, Day 14 (2W), Day 28 (4 W), Day 42 (6W) Day 84 (12 W), Day 182 (26 W) and Day 365 (52 W) 7. Safety assessment of OsStic resorption determined from CT imaging [Discharge, Day 42 (6W) and Day 365 (52 W)] 8. Incidence of wound complications by Day 182 (26 W) post primary surgery. 9. Incidence of metalwork failure or secondary collapse at the fracture site by Day 42 (6 W) and Day 365 (52 W) post primary surgery. 10. Incidence of other adverse events related to study procedure by Day 42 (6 W) and Day 365 (52 W) post primary surgery.
Exploratory / Other endpoints	Range of Motion, Patient Satisfaction, Surgeon Satisfaction and ease of use.
Statistical Analysis	A descriptive analysis of safety and performance variables will be performed. The descriptive analyses will be performed to describe: nature of adverse events, their distribution and frequency. Moreover, all factors which may appear predictive for the rate of adverse events will be analyzed (age, sex, dimension of the implanted device, system used, diabetes history, smoking habits, alcohol consumption, concomitant treatments/diseases, other). If the proportion of patients experiencing a device-related adverse event is sufficiently large relative to the overall sample (≥70%), the time interval between the date of surgery and the first occurrence of an adverse event will be evaluated. In this case, the median time to first adverse event, with a 95% confidence interval, will be estimated using Kaplan–Meier survival analysis. An adaptive interim analysis will be performed when at least 5 Patients have completed the V7 visit. An independent Data Safety Monitoring Board (DSMB) will review the results of the interim analysis, with respect to the primary endpoint (safety), and provide one of the following recommendations to the Sponsor: • stop the study for unacceptable safety concern; • continue the study up to 15 Patients completed. DSMB will receive all safety data periodically and data on Serious Adverse Events (SAE) as soon as reported.

Investigational Sites	Trauma & Orthopaedic Surgery - School of Medicine University of Leeds, UK

2.0 Schedule of Activities

Assessment	V1	V2	V3	V4	V5	V6	V7	V8	V-9
	D -7	D 0	D 7 +/-3 (1W)	D 14 +/-3 (2W)	D 28 +/-3 (4W)	D 42 +/-3 (6W)	D 84 +/-7 (12W)	D 182 +/-14 (26W)	D 365 +/-28 (52 W)
LEEDS attendance trauma clinic			X	X	X	X	X	X	X
Screening and Informed Consent collection	X								
Device implantation: application of OsStic BVF implant at Surgical site; Evaluation of Technical Success; Ease of Use Questionnaire		X							
AP & LAT x-rays of the knee to determine RRS Score			X			X	X	X	X
Numeric Pain Rating Scale for pain while weight bearing: FIX-IT Measure						X	X	X	
CT scan of the knee for safety and evaluate OsStic resorption.	X		X[1]			X[1]			X[1]
Load, Gait and Balance (std protocol) using XSENSOR insoles			X	X	X	X	X		
Adverse events/ safety assessment variables/ Wound checks			X			X		X	X
Numeric Pain Rating Scale for pain			X	X	X	X	X	X	X
SF-12v2™ + EQ-5D™			X			X	X	X	X
Pain relief medications, Telephone/Postal questionnaire review			X	X	X	X	X	X	X

[1] CT imaging will compare images at discharge 6 weeks and 52 weeks to evaluate OsStic BVF resorption.

3.0 Supporting Documentation

Document	Document Title
BMI-DHF-23-001-D-032	Clinical Investigation Plan for OsStic's First in Human Clinical Trial.
BMI-DHF-23-001-D-033	Clinical Investigators Brochure for OsStic's First in Human Clinical Trial.