PROTOCOL HISTORY

CLINICAL TRIAL PROTOCOL

TITLE	A first-in-human proof-of-concept study with NVDX3, an osteogenic implant of human allogenic origin, in the treatment of distal radius fractures in adults.
PROTOCOL NUMBER	NVDX3-CLN01
VERSION NUMBER	V6.0
PROTOCOL DATE	25-JUNE-2023
AMENDMENT NUMBER	NA
EUDRACT NUMBER	2022-002304-21
INVESTIGATIONAL MEDICINAL PRODUCT	NVDX3
CHIEF MEDICAL OFFICER	[redacted] Novadip Biosciences Watson & Crick Hill Rue Granbonpré 11 1435 Mont-Saint-Guibert - Belgium Phone: +32 (10) 77 92 20 [redacted]
SPONSOR	Novadip Biosciences Watson & Crick Hill Rue Granbonpré 11 1435 Mont-Saint-Guibert – Belgium

Protocol Version	Protocol Date	Protocol Amendment #	Type of Amendment
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Protocol V6.0	*25-June-2023*	*NA*	*Not applicable*

[redacted]

[redacted]

[redacted]

[redacted]

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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT - PIPA

To be completed by all PIs participating in the trial

PROTOCOL TITLE A first-in-human proof-of-concept study with NVDX3, an osteogenic implant of human allogenic origin, in the treatment of distal radius fractures in adults.

EUDRACT NUMBER	2022-002304-21
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VERSION NUMBER	V6.0
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SPONSOR	Novadip Biosciences

I have read the protocol specified above and I will conduct the trial as outlined herein. In my formal capacity as Investigator, my duties include ensuring the safety of the trial patients enrolled under my supervision and providing the Sponsor with complete and timely information, as outlined in the protocol.

I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the IEC, and Health Authorities, except where necessary to prevent immediate danger to the patient. It is understood that all information pertaining to the trial will be held strictly confidential and that this confidentiality requirement applies to all trial staff at this site.

Furthermore, on behalf of the trial staff and myself, I agree to maintain the procedures required to carry out the protocol and any approved protocol amendments in accordance with

- The International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP E6) current version
- Committee for Medicinal Products for Human Use (CHMP) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products - 20 July 2017 EMEA/CHMP/SWP/28367/07 Rev. 1
- Guideline on safety and efficacy follow-up- Risk management of advanced therapy medicinal products – EMEA/149995/2008
- The Declaration of Helsinki, version 1996 and subsequent amendments
- All other applicable regulatory requirements and national legislation

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

_____

INVESTIGATOR NAME

_____ _____

DATE INVESTIGATOR SIGNATURE

SPONSOR PROTOCOL APPROVAL SIGNATURES - SPAS

To be completed by the Sponsor's protocol approvers

PROTOCOL TITLE A first-in-human proof-of-concept study with NVDX3, an osteogenic implant of human allogenic origin, in the treatment of distal radius fractures in adults.

EUDRACT NUMBER	2022-002304-21
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SPONSOR	Novadip Biosciences

[redacted]

[redacted]

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NAME

_____

DATE

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SIGNATURE

LIST OF ABBREVIATIONS

AAOS	American Academy of Orthopedic Surgeons
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AP	Antero-Posterior
ATMP	Advanced Therapy Medicinal Product
ASC	Adipose (Mesenchymal) Stem Cell
BMP	Bone Morphogenic Protein
BP	Blood Pressure
βTCP	Beta-Tricalcium Phosphate
CA	Competent Authority
CHMP	Committee for Medicinal Products for Human Use
COLX	Type X Collagen
CTNNB1	b-catenin
CRF	Case Report Form
CT	Computed Tomography
DECT	Dual Energy Computed Tomography Scans
DLP	Dose Length Product
DP	Drug Product
DRF	Distal Radius Fractures
DS	Drug Substance
cc	Cubic centimeter
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ED	Effective Dose
EF	External Fixation
EMA	European Medicines Agency
ETV	Early Termination Visit
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
Fl	Flerovium
FPFV	First Patient First Visit
g	Grams
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (EU) 2016/679
h	hours
HA	Hydroxyapatite
βTCP	beta-tricalcium phosphate
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B surface Antigen

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD	Hospital Discharge
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICH E6 GCP	International Conference on Harmonization Guidance for Industry, Good Clinical Practice: Consolidated Guidance
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Nonproprietary Names
IGF1	Insulin-like growth factor 1
IS	Implant Surgery
keV	kiloelectron Volt
kVp	kiloVolt peak
LAT	Lateral
LPLV	Last Patient last Visit
M	Month
MCR	Metaphyseal collapse ratio
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
mGy.cm	Milligray per centimeter
MMWS	Modified Mayo Wrist Score
mSv	Millisievert
NA	Not Applicable
NRS	Numeric Rating Scale
NVD	Novadip
OB	Leptin
OPG	Osteoprotegerin
OTA	Orthopedic Trauma Association
PI	Principal Investigator
PIPA	Principal Investigator Protocol Agreement
PoC	Proof-of-Concept
PT	Preferred Term
rAESI	Reportable Adverse Event of Special Interest
PRO	Patient Reported Outcomes
PRWE	Patient-Rated Wrist Evaluation
QA	Quality Assurance
QC	Quality Control
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SDV	Source Data Verification
Si	Silicium
SoCa	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAS	Sponsor Protocol Approval Signature
Sr	Strontium
TEAE	Treatment Emergent AE
TMP	Trial Monitoring Plan
V	Visit
VEGF	Vascular Endothelial Growth Factor
W	Week
WOCBP	Women Of Child Bearing Potential

PROTOCOL SYNOPSIS

Title: A first-in-human proof-of-concept (PoC) study with NVDX3, an osteogenic implant of human allogenic origin, in the treatment of distal radius fractures in adults.

Study description: A single arm, monocentric study in adult patients, suffering from a distal radius fracture, treated during the osteosynthesis intervention with NVDX3.

After the Implant Surgery (IS) the safety follow-up will cover two distinct stages followed by a long-term safety follow-up study:

- Phase 1: Acute safety phase up to 6 weeks post-IS (W6)
- Phase 2: Long-term safety follow-up from W6 up to of 12-month post-IS
- NVDX3-CLN0X: NVDX3 long-term safety study up to 10 years post-NVDX3-CLN01 study

Study Objectives and endpoints:

	Objectives	***Endpoints***
Primary	**Safety**: To assess the safety of the NVDX3 implant in an orthotopic environment	• Description of all SAEs and NVDX3 related AEs between screening (V1) and 12-months post-IS.

Secondary	**Safety**:
	To assess the acute- and long-term safety of the NVDX3 implant
		• Description of all acute SAEs and NVDX3 related AEs between screening (V1) and 6 weeks post-IS (V5).
		• Description of all SAEs and NVDX3 related AEs beyond 6 weeks (V5 excluded) until 12 months post-IS
		• Description of Treatment Emergent AEs (TEAEs) for the periods:
		  ◦ Between screening and week 6 (V5 included)
		  ◦ Between week 6 (V5 excluded) and month 12 (V8 included)
		  ◦ Full study duration
		• Description of related and unexpected (S)AEs between inclusion and study completion

		• Description of AE of Special Interest (AESI) between inclusion and study completion • Description of lab data and vital signs obtained between inclusion and study completion
	Efficacy: To assess the efficacy of the NVDX3 implant radiologically and clinically	• Description of bone formation status a, 3-, and 12-months post-IS compared to hospital discharge (HD) based on Computed Tomography scans (CT) and at HD, 2-, 6-weeks, 3-,6-, and 12-months post-IS compared to the peri-operative x-ray acquisitions • Description of bone union status at 3-, and 12-months post-IS compared to HD based on Computed Tomography scans (CT) and at HD, 2-, 6-weeks, 3-,6-, and 12-months post-IS compared to the peri-operative x-ray acquisitions • Description of bone remodeling status at , 3-, and 12-months post-IS compared to HD based on Computed Tomography scans (CT) and at HD, 2-, 6-weeks, 3-, 6-, and 12-months post-IS compared to the peri-operative x-ray acquisitions • Description of Total extended Lane and Sandhu Score at 3-, and 12-months post-IS compared to HD based on Computed Tomography scans (CT) and at HD, 2-, 6-weeks, 3-,6-, and 12-months post-IS compared to the peri-operative x-ray acquisitions • Description of the patient's clinical status and evolution at 2-, 6 weeks, 3-, 6-, and 12-months post-IS compared to HD using: o Grip Strength measure o Modified Mayo Wrist Score (MMWS) o Patient-Rated Wrist Evaluation questionnaire (PRWE) • Description of the patient's pain status and evolution via Numeric Rating Scale pain

		(NRS-pain) at HD, 2-, 6 weeks, 3-, 6-, and 12-months post-IS compared to screening using:
Exploratory	[redacted]	[redacted]

Study Population: 10 adult male and/or female patients with a native intra-articular Distal Radius Fracture (DRF).

Phase: PhI/IIa Study **(**First-in-human proof-of-concept)

Description of Sites/Facilities Enrolling Patients:

This trial will be conducted by orthopedic surgeons

Description of Study Treatment:

NVDX3 is an osteogenic implant of human allogenic origin. This lyophilized and sterilized tissue engineered product is composed of extracellular matrix, biologically active growth factors and biomolecules, non-viable osteogenic cells associated with hydroxyapatite/beta-tricalcium phosphate (HA/TCP) particles. NVDX3 is formulated as a lyophilized powder, sterilized by gamma radiation.

NVD-X3 off-the-shelf implant is intended to induce bone formation between two bone segments [redacted] As well in an orthotopic as in a heterotopic environment.

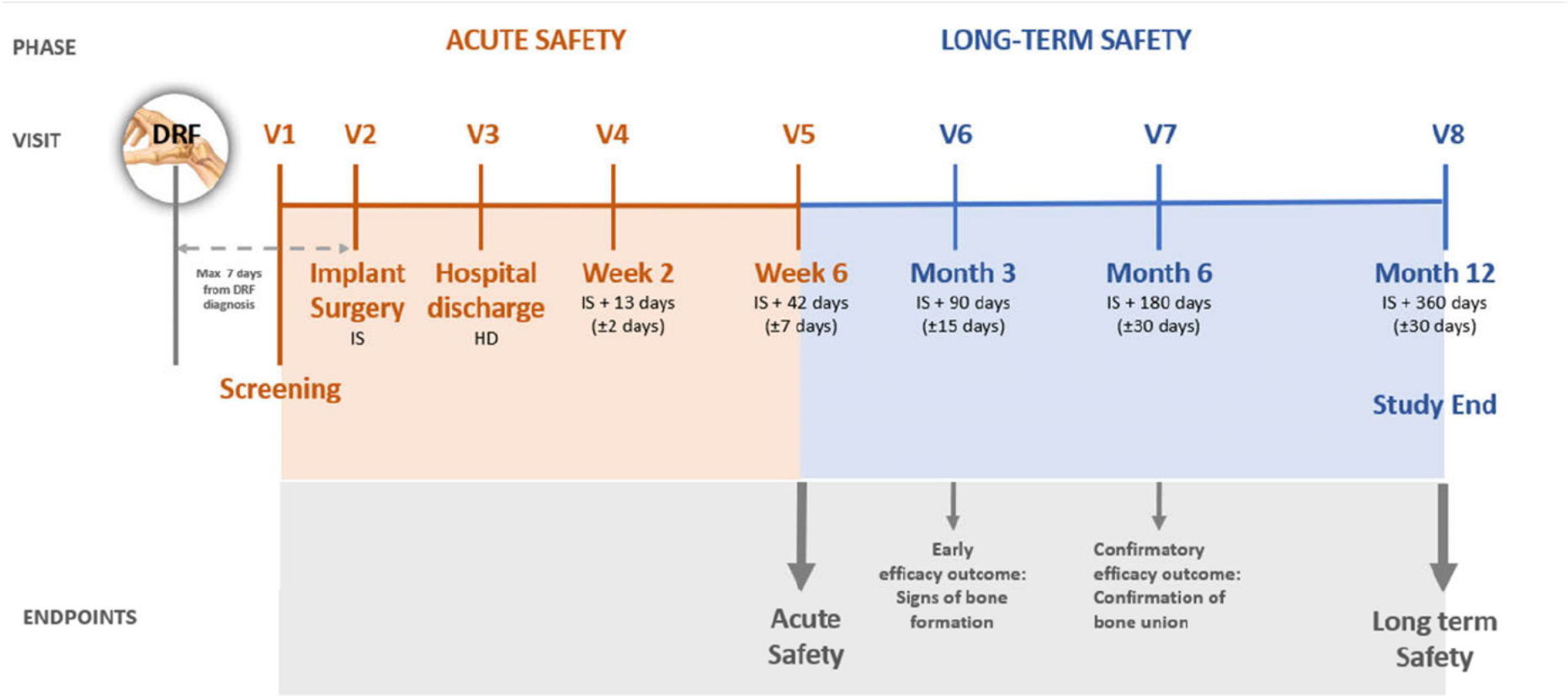
Study Duration: ***Protocol NVDX3-CLN01:*** Approximately 15 months. (From FPFV to LPLV)

Protocol NVDX3-CLN0X: *Up to 10 years after the LPLV in the NVDX3-CLN01 study*

Patient Duration: ***Protocol NVDX3-CLN01:*** Approximately 13 months (From DRF diagnosis to the 12-months post-implant surgery)

Protocol NVDX3-CLN0X: *Up to 10 years after the patient's last visit in the NVDX3-CLN01 study*

TRIAL DESIGN SCHEME



1. INTRODUCTION

1.1. Background of Information and scientific rationale

1.1.1. Background information

A. NVDX3

NVDX3 is an osteogenic implant of human allogenic origin. This tissue engineered product is composed of extracellular matrix, biologically active growth factors and biomolecules, non-viable osteogenic cells associated with hydroxyapatite/beta-tricalcium phosphate (HA/TCP) particles. NVDX3 is formulated as a lyophilized powder, sterilized by gamma radiation.

NVD-X3 off-the-shelf implant (powder for reconstitution) is intended to induce bone formation between two bone segments as well in an orthotopic as heterotopic environment. The pro-osteogenic and anti-resorptive properties of the stem cell-derived biomolecules are driving the bone formation.
It can be postulated that NVDX3's mode of action is based on:

I. The high degree of mineralization contributing to the direct formation of a hard bone callus,
II. the promotion of angiogenesis with specific biological growth factors,
III. the induction of osteogenesis (endochondral ossification) with specific biomolecules and,
IV. the release of molecules implied in the control of the osteoclasts activity to reduce the bone resorption after implantation.

For more detailed information on the mode of action of NVDX3, please refer to the latest version of the IB.

B. Targeted indication: Distal radius fracture

Description

Fractures of the distal radius (DRF), often referred to as "wrist fractures", are common in both children and adults. Most of the fractures are caused by a fall on the outstretched hand with the wrist in dorsiflexion. They are usually occurring in the distal radius within three centimeters of the radiocarpal joint. Most of these traumatic incidents are closed injuries, the overlying skin remaining intact.

Acute DRF results in pain, limitations in disability stress, and the potential inability to work. Delayed fracture healing permanent loss in function, or continuous pain may cause substantial morbidity and impact on social and professional activities.

Incidence

DRF is one of the most common fractures with an incidence of 195.2/100,000 persons per year[1]. The distributive pattern of these injuries is bimodal, affecting young (predominantly male) adults through high-energy falls and elderly (predominantly female) adults through low-energy falls

and presence of osteoporosis. Besides age (e.g. older women with osteoporosis) and gender (e.g. young males), lifestyle such as playing/sporting activities and motor vehicle accidents also has an impact of the risk ratio of DRF[1-3].

Classification and quantification metaphyseal comminution and fracture instability (see also Appendix 1)

The OTA (Orthopeadic Trauma Association) is the most widely adopted classification for fractures and dislocations. It defines the fracture based on localization, type, fracture pattern and geometry[4].

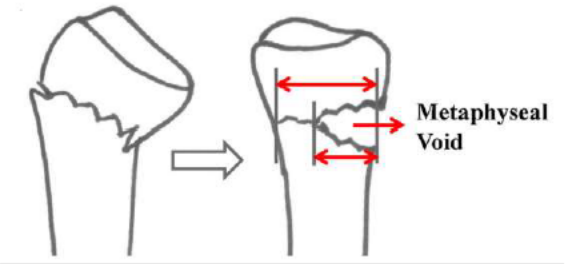
Frykman established a classification system that identifies involvement of radio-ulnar and radio-carpal joints along with the presence or absence of ulnar styloid involvement. Although many authors have accepted this classification, this system does not include the extent of initial displacements and comminution[5].

More recent classification systems have focused on the mechanism of injury. Melone reflected on both the mechanism and degree of injury to distal radius (excluding distal ulna) and the classification for selection of treatment. This system sets the importance of the medial portion of articular column of the distal aspect of the radius for determining prognosis and treatment options[6].

In 1993, Fernandez published a specified classification that separates the fractures of the distal end of the radius according to the mechanism of injury[7].

Metaphyseal comminution (Figure 1) is widely considered as a key radiographic parameter that predicts fracture instability for DRFs. To quantify this metaphyseal void defect objectively, the validated metaphyseal collapse ratio has been developed and validated[8].

Figure 1: Metaphyseal comminution



The volume of the metaphyseal defect is estimated from perioperative X-rays.

1. The metaphyseal defect is a rectangular hexahedron and is calculated by measuring the length and width on the posteroanterior radiograph and the height on the lateral radiograph.
2. The degree of reduction will be assessed by measuring radial inclination, volar angulation, and ulnar variance. Radial inclination and volar angulation will be measured by using the method described by Goldfarb et al., and ulnar variance will be measured with the method described by Medoff. A loss of reduction is defined as dorsal angulation

of >10, volar angulation of >20, an articular gap or step-off of >2 mm, or radial inclination of <10[9-11].

3. The metaphyseal collapse ratio (MCR), expressing the maximal radiolucent extent as a percentage of the intercortical distance, will be used to quantify metaphyseal comminution[8].

Treatment

The aim of treatment is pain relief and return of function while weighing the risks and benefits of nonoperative and operative treatment. There are multiple treatment options, including closed reduction and cast immobilization, percutaneous K-wire fixation, fixation with volar or dorsal plates (locking or nonlocking), bridge plating, use of an external fixator, or a combination of these techniques. Although the best choice depends to some extent on the characteristics of the fracture (open/closed, nondisplaced/displaced, extra-/intraarticular), there is little high-quality evidence to inform this decision-making. The clinical practice guidelines for DRF published by the American Academy of Orthopaedic Surgeons (AAOS) made 29 recommendations; however, none of these recommendations was given a ‘‘strong’’ rating owing to limited strength of the evidence[12,13].

Volar plating is widely used because of its stability, early movement, and quick return to activity. This technique allows to perform a satisfactory surgical treatment in almost every kind of wrist fracture with a low complication rate providing an immediate stable fixation and distal radius fragment collapse prevention, even in most severe osteoporotic cases[14]. Dorsal plating may be preferred for buttressing of comminuted fractures, but risks extensor tendon injury. Percutaneous pins are a less invasive, cheaper surgical option, but may lack stability. External fixation is another less invasive procedure and may be augmented with Kirschner-wires for added stability. Casting is less costly and avoids surgical complications but may not provide adequate reduction. Several treatment methods for DRFs have been proven effective, but none have emerged as a clear treatment of choice[14].

Particularly in people with osteoporotic bone, metaphyseal comminution and/or high impaction may result in a bony void in the distal radius that may be associated with loss of reduction and malunion. This defect can be filled with some biocompatible material; for example, an autograft (autogenous bone graft) that is obtained from the patients themselves. Such bone is ’harvested’ or extracted from a donor site; usually the iliac crest (a part of the pelvic girdle). However, autograft harvesting carries a significant risk of complication, including donor site pain, haematoma, infection and nerve injury[15]. Besides donor site comorbidity prolonged intervention time due to the need to perform the graft harvesting, graft resorption, molding challenges and limited availability of grafting material, especially in pediatric patients, have been described extensively as potential hurdles linked to the use of autologous bone[16].

A common alternative is an allograft (allogenic bone graft), obtained from cadaveric donors or live donors undergoing procedures such as total hip replacement. Allografts are osteoconductive and weakly osteoinductive, though there are still concerns about the residual infective risks, costs and donor availability issues. As an alternative, xenograft substitutes are cheap, but their use provided contrasting results, so far. Ceramic-based synthetic bone substitutes are alternatively

based on hydroxyapatite (HA) and tricalcium phosphates, and are widely used in the clinical practice. Indeed, despite being completely resorbable and weaker than cortical bone, they have exhaustively proved to be effective. Biomimetic HA are the evolution of traditional HA and contains ions (carbonates, Si, Sr, Fl, Mg) that mimic natural HA (biomimetic HA). Injectable cements represent another evolution, enabling minimal invasive techniques. Bone morphogenetic proteins (namely BMP2 and 7) are the only bone inducing growth factors approved for human use but only in spine surgery and for the treatment of tibial nonunion. Demineralized bone matrix and platelet rich plasma did not prove to be effective and their use as bone substitutes remains[17].

Experimental cell-based approaches are considered the best suitable emerging strategies in several regenerative medicine application, including bone regeneration. In particular, mesenchymal stem cells have been widely exploited for this purpose, being multipotent cells capable of efficient osteogenic potential[18].

Conclusion

Within the DRF indication, the metaphyseal comminution remains an important challenge. Autologous bone grafting is still considered the most effective material to fill the metaphyseal defect. Alternatives to autologous bone grafts lack one or more of the properties described in the ‘‘Diamond theory’’ of Giannoudis: osteogenic cells and vascularization, mechanical stability, growth factors, osteoconductive scaffolds (in combination with growths factors), being the prerequisite for bone healing[19].

1.1.2. Study Rationale

DRF was chosen as a clean model for exploring the bone formation potential of the NVDX3 implant in a heterotopic environment. High impact metaphyseal comminution DRFs are underappreciated injuries and are a common cause of chronic wrist pain and limited range of motion, negatively impacting the quality of life of the patients.

Autologous bone graft extracted mostly from the patient’s iliac crest, currently considered as the standard of care to fill the metaphyseal defect, carry a significant risk of complications, including donor site pain, haematoma, infection and nerve injury[15]. It also prolongs the duration of the intervention considerably. Additionally other associated complications such as graft resorption, molding challenges and limited availability of grafting material, can be potential hurdles for this technique[16].

MSC therapy has attracted attention due to the potential to improve the treatment outcome by promoting bone formation[18]. Based on the currently available pre-clinical data, NVDX3 has shown to be a potential alternative for both autologous bone and ceramic-based synthetic bone substitutes.

1.2. Risks/benefits assessment

1.2.1. Potential risks

Potential Risk		Comments
NVDX3	- First-in-human administration	Pre-clinically no NVDX3 related safety signals were observed. Updated safety information on NVDX3 can be consulted in the latest version of the IB.
DRF Surgery	- tendon irritation and rupture, nerve injury, malunion, nonunion, pain syndromes, loss of reduction, and posttraumatic arthritis	The surgical procedure, aiming fixation of the DRF will be performed as per standard of care of the clinical site.
General Surgery	- pain, local infection, thrombosis of the veins and orthostatic hypotension.	Prophylactic use of antalgics, prophylactic antibiotics, anticoagulants, and fluids might reduce their occurrence and frequency.
Imaging	- Risks linked to the medications given prior and during any of the study procedures	Well-known risks related to the use of sedatives, analgesics and anaesthetics
	- Radiation exposure	- DECT considered to be dose-neutral compared to conventional CT
		- Estimated radiation increase compared to SoCa imaging protocol for DRF remains limited

Risks related to the study product:

Pre-clinical in vitro and in vivo studies on safety, mutagenicity, tumourigenicity, immunotoxicity and immunogenicity support that NVDX3 is safe, non tumourigenic and has very low to no immunogenic potential. No NVDX3 related side effects have been observed during the pre-clinical development. For any updates on observed risks related to NVDX3, please refer to the latest version of the Investigators Brochure (IB)

Despite the positive safety profile set during pre-clinical development, the following events cannot formally be excluded due to the allogeneic and the ATMP nature of the product (ref. recommendations of the CHMP "Guideline on safety and efficacy follow-up- Risk management of advanced therapy medicinal products – EMEA/149995/2008"):

1. Immune reactions including but not limited to fever, local or systemic allergic reactions, redness of the skin, implant site infection and graft rejection. Immunogenic site effects will receive special attention and will be followed closely through safety lab analyses up to 6 months post-grafting surgery.

2. Due to a detection limit of the applied analytical methods, the presence of viable donor cells and related potential abnormal activity cannot completely be ruled out. This will be closely evaluated radiologically and clinically at each follow-up visit of this study and during the long-term safety study (NVDX3-CLN0X).

Other historically reported risks related to ATMPs (but not observed for NVDX3) defined within the recommendations of the CHMP ("Guideline on safety and efficacy follow-up- Risk management of advanced therapy medicinal products – EMEA/149995/2008"), have been addressed more in detail in the latest version of the IB.

Risks related to the study procedures:

- **DRF Surgery**

The surgical procedure, aiming fixation of the DRF will be performed as per standard of care of the clinical site (including the associated blood draws and sedative/anesthetic procedures).

Although most patients do well with current fixation techniques, complications cannot be excluded[20]. Besides tendon irritation and rupture, nerve injury, malunion, nonunion, pain syndromes, loss of reduction, and posttraumatic arthritis must all be considered when treating DRFs

- **Imaging protocol**

Based on literature with HA[21] [redacted] a high radiopacity was observed related to the high mineral content. This opacity presents a challenge for the radiological evaluation of X-ray images. Consequently, the follow-up of the patients in this study would require CT imaging allowing a better visualization of the bone formation effect of NVDX3. The sponsor even introduced the use of DECT scans allowing, besides reducing metal and beam hardening artifacts, to investigate in much more detail the NVDX3 characteristics and efficacy parameters (see also Appendix 2).

Today, literature considers DECT to be dose-neutral compared to conventional CT. Effective dose (ED) (expressed in millisievert or mSv) to patients can be estimated by using dose length product DLP (mGy.cm) to effective dose (ED) conversion coefficients. The DLP represents the amount of radiation which is used for the exposure and is recorded by the scanner. Koivisto et al and Biswas et al reported an effective dose to scans of the wrist of respectively 0.001mSv and 0.03mSv22. As per request of the Luxembourg Ministry of Health, and conform to art.78 of the Luxembourg Law on radioprotection, a radiation exposure estimation has been completed by an expert on radioprotection of the Federation of Hospitals in Luxembourg (FHL). In this context, a series of lower arm phantom scans have been completed including samples of the targeted IMP. The FHL report called "Avis d'expert en physique medical concernant l'étude clinique was completed on 27JAN2023 and submitted to the Luxembourg Health Authorities.

As a conclusion, the average estimated DLP was 135,34 ± 41,74 mGy.cm, approximately corresponding to 0.05mSv when applying 0,00037 mSv/mGy.cm as conversion factor. The assessments of the 22.

In general, doses from scans of the extremities, compared to chest, abdomen, pelvis and spinal scans, remain at the very low level of the diagnostic dose range due to the absence of major radiosensitive organs within the scan range [23,24].

As calculated, a typical DLP of the wrist/hand scan is 135 mGy.cm (Table 1). This will result in an effective dose of approximately 0.05 mSv for adults.

When evaluating radiation exposure over the total of 12 months follow-up, the expected effective dose would not exceed 0.2 mSv. Comparing the proposed study protocol with the standard of care, shows a limited radiation increase with about 0,152 mSv over a total observation period of 12 months (Table 1).

Knowing that normal background radiation reaches about 3 mSv per year, an increase of about 0.15 mSv per year probably has low clinical relevance[23].

Additionally, based on the obtained FHL report the most optimized acquisition parameters will be applied to minimize the radiation exposure further reducing the total radiation exposure for the study to 0,120mSv introducing another dose reduction of 0,032mSv. These most optimal parameters (including kV, mAseff tube A, rotation time, P, Collimation, Ep/lc, L and algorithm) have been included in the imaging acquisition manual.

Table 1: Estimated radiation for an adult patient: Study schedule compared to SoCa

Visit		V1	V2	V3	V4	V5	V6	V7	V8	TOTAL
		Screening	IS	HD	W2	W6	M3	M6	M12	
Study protocol	X-Ray (AP/LAT)	0.001	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.209
	CT	0.05								
	DECT			0.05			0.05		0.05	
SoCa*	X-Ray	0.001	0.002	0.001	0.001	0.001	0.001			0.057
	CT	0.05								
Difference Study vs SoCa		0	0	0.05	0	0	0.05	0.001	0.051	0.152

SoCa: Standard of Care; Y: Year; V: Visit; mSv: millisievert; CT: Computed Tomography; DECT: Dual Energy CT scan; IS: Implant Surgery; HD: Hospital discharge; W: week; M: Month

*SoCa: SoCa of diagnostic, peri-and post-operative management at the CHLsupported by the PI and appointed radiologist (see also statement letters supporting the SoCA imaging and radiation exposure letters).

1.2.2. Known potential benefits

- **Avoid bone graft harvesting and its related comorbidities**

  The use of NVDX3 eliminates the need for an invasive and cumbersome iliac crest harvesting along with its known risks and complications [16,25-31].

  - Prolonged intervention time due to the need to perform the graft harvesting.
  - Peri- and post-operative complications like injury of the physis, pain, nerve damage, and wound healing complications such as bleeding, hematoma and infection.
  - Graft resorption.
  - Application/molding challenges.
  - Limited availability of autologous bone graft material. NVDX3, in the contrary, is manufactured in a controlled setting, guaranteeing the graft quantities needed to cover the surgical needs.

- **No need to add scaffolds/carriers**

  The use of NVDX3 does not require an additional scaffold or carrier (eg. Collagen sponge) and consequently eliminates their associated potential side effects (e.g., hypersensitivity reactions).

- **No need to add bone modulating agents**

  Since NVDX3 has the potential to promote osteogenesis the addition of other bone modulating agents, such as BMP and bisphosphonates is not required, eliminating the risk of associated side effects and contraindications.

1.2.3. Conclusion risk/benefit assessment

Based on the pre-clinical information, the implant procedure, and the expected osteogenic induction properties of IMP, NVDX3 can be considered to have a beneficial risk/benefit profile for use in human

For the latest updates on potential risks and benefits linked to NVDX3 refer yourself to the latest version of the Investigator Brochure (IB).

2. OBJECTIVES AND PURPOSE

2.1. Objectives

This PoC study will assess the safety and the efficacy of NVDX3 supporting orthotopic ossification[1] in adult patients suffering from a Distal Radius Fracture (DRF).

Primary objective:

- To assess the safety of the NVDX3 implant

Secondary objectives

- To assess the acute and long-term safety of the NVDX3 implant
- To assess the efficacy of the NVDX3 implant radiologically and clinically
- To explore and evaluate new radiological assessment methods for NVDX3

2.2. Purpose

The NVDX3-CLN01 study is designed as a first in human PoC aiming at assessing the safety and preliminary efficacy of the NVDX3 implant in an orthotopic bone fusion indication, i.e long bone non-union or DRF.

[1] Orthotopic bone formation refers to the presence of bone formation occurring at a normal place in the body, pertaining to a tissue transplant grafted within existing bone. In this study context, including distal radius fracture, bone formation is induced to fill the bone void induced by the trauma.

3. STUDY DESIGN AND ENDPOINTS

3.1. Description of the study design

This is a prospective, single arm, monocentric first-in-human PoC study in adult patients, suffering from a distal radius fracture, treated during the surgical intervention with NVDX3, an osteogenic implant from human allogeneic origin.

As per standard of care, patients with DRF are followed up to 3 months post-intervention. In the context of this trial, patient safety and IMP efficacy will be followed up to 12 months post-implant surgery.

At the end of this study, the included patients will be invited to participate in a long-term safety follow-up study for an additional period of 10 years.

3.2. Study endpoints

Primary Endpoint

Evaluation of all SAEs and NVDX3 related AEs between screening (V1) and 12-months post-IS (V8).

Secondary Endpoints

Safety

1. Description of all acute SAEs and NVDX3 related AEs between screening (V1) and 6 weeks post-IS (V5).
2. Description of all SAEs and NVDX3 related AEs beyond 6 weeks (V5 excluded) until 12 months post-IS
3. Description of Treatment Emergent AEs (TEAEs) for the periods:
    a. Between screening and week 6 (V5 included)
    b. Between week 6 (V5 excluded) till month 12 (V8 included)
    c. Full study duration
4. Description of related and unexpected (S)AEs between inclusion and study completion
5. Description of AE of Special Interest (AESI) between inclusion and study completion
6. Description of lab data and vital signs obtained between inclusion and study completion

Efficacy

- **Radiological assessments on Computed Tomography data (CT[2]) using the extended Lane and Sandhu Scoring tool (eLSS)**

The following assessments will be performed at 3and 12-months post-IS compared to HD

1. Evaluation of bone formation status
2. Evaluation of bone union status
3. Evaluation of bone remodeling status
4. Evaluation of Total extended Lane and Sandhu Score

- **Radiological assessments on X-ray Using the eLSS tool**

The following assessments will be performed at HD, 2-, 6-weeks, 3-,6- and 12-months post-IS compared to the peri-operative x-ray acquisitions

1. Evaluation of bone formation status
2. Evaluation of bone union status
3. Evaluation of bone remodeling status
4. Evaluation of Total extended Lane and Sandhu Score

- **Clinical assessments**

The following assessments will be performed at 2-,6 weeks, 3-, 6-, and 12-months post-IS compared to HD:

1. Grip strength measure with a hydraulic hand dynamometer
2. Modified Mayo Wrist Score (MMWS): A physician-based scoring evaluating the patients' pain, active flexion/extension arc, grip strength and ability to return to regular employment or activities.
3. PRWE Questionnaire: A patient reported scoring evaluating the patients' wrist pain and disability

NRS-pain, a patient reported scoring evaluating the patients' pain, will be performed at HD, 2-,6 weeks, 3-, 6-, and 12-months post-IS compared to Screening.

[2] As per imaging requirements Dual energy CT (DECT) acquisitions will be obtained. The DECT acquisition also contains the core data of the "normal" CT, enabling to filter and evaluate CT images separately.

Exploratory endpoints

- [redacted]

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Inclusion criteria

Patients must meet all the inclusion criteria to be eligible to participate in the study:

1. Male or female patients within the age range of ≥18 years to ≤80 years.
2. Patient diagnosed with DRF **with confirmed**:
    a. Classification AO/ATO: C2 and C3 - Intra-articular & multifragmentation.
    b. Estimated volume of the targeted bone void should not exceed 5cc.
    c. Availability of diagnostic AP and LAT X-ray or CT scan.
3. Patient can undergo the targeted surgical intervention within 7 days post-DRF diagnosis.
4. Patient fulfills criteria for undergoing a surgical intervention.
5. Patient has understood and accepted to participate in the study according to all study procedures by signing the informed consent.

4.2. Exclusion criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

1. Open DRF or closed DRF with increased infection risk.
2. Injury to the median nerve.
3. Previous fracture of the target distal radius.
4. Documented disease limiting mobility and functional assessments (eg. Grip strength test).
5. Dependency on crutches or any comparable walking aids.
6. Patient is overweight, has a BMI ≥35.
7. Presence of clinically significant infection at the target implant site or systemic infection.
8. History of allergic reaction or any anticipated hypersensitivity to any of the anticipated:
    a. Osteosynthesis materials (PEEK plate and screws).
    b. Anesthetic agents.
    c. Components of the NVDX3 implant.
9. Presence of any auto-immune disease, with exception of well controlled diabetes type-1 or II, or auto-immune thyroid disorders.
10. Positive serology for human immunodeficiency virus (HIV), HBcAb and/or HBsAg.
11. Presence of an active tumor.
12. Documented metabolic bone disease or any disorder, such as but not limited to high-risk osteoporosis, that could interfere with the bone healing and bone metabolism.

13. Chronic, ongoing, or planned use of medications that might affect bone metabolism or bone quality such as bisphosphonates, steroids, methotrexate, anticoagulants, immunosuppressants or immunotherapy.
14. Excessive smoking, history of chronic alcohol or drug abuse within the 12 months prior to screening.
15. Any history of experimental therapy with another investigational drug within 60 days prior to screening.
16. Pregnant women or women of childbearing potential (WOCBP) not agreeing to use an effective method of birth control[3] during the course of the study. Note: WOCBP including peri-menopausal women who have had a menstrual period within 1 year prior to surgery have to have a negative pregnancy test before entering in the study.
17. Any other psychosocial, mental, and physical condition which, in the opinion of the investigator, could interfere with the trial conduct, the patient's compliance or influence interpretation of the results.
18. Patient with historically elevated radiation exposure levels that could in the opinion of the investigator introduce unacceptable radiation risks for the patient, when being accumulated with the radiological examinations planned in this study.

4.3. Strategy for recruitment and retention

It is intended to enroll 10 evaluable patients. A patient is considered evaluable once he/she underwent the implant surgery with NVDX3. Non-evaluable patients will be replaced.

No specific recruitment activities are envisioned.

4.4. Participant withdrawal or termination

4.4.1. Reason for withdrawal or termination

All patient included will be followed for safety and efficacy assessments throughout the complete duration of the study unless the patient withdraws his/her consent. The patient and/or legal guardian(s) are free to withdraw from participation in the trial at any time without prejudice to their continued care and without any need for justification.

[3] an effective method of birth control is defined as a method which results in a failure rate of less than 1% per year such as combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), Intrauterine device (IUD), Intrauterine hormone-releasing system (IUS), Bilateral tubal occlusion, Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the surgical success of vasectomy has been confirmed), Sexual abstinence

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant develops an illness that would interfere with his/her continued participation.
2. Participant is noncompliant with the study procedures or medications in the opinion of the investigator.
3. Participant takes prohibited concomitant medications (that are not prescribed by the investigator) as defined in this protocol.
4. Participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The sponsor or a regulatory agency requests withdrawal of the participant.

Note: An eligible study participant who withdraw or was withdrawn from the study will not be replaced

4.4.2. Handling of participant withdrawals or early termination

The Investigator should document the primary reason for a patient´s premature withdrawal from the trial, in the patient file and in the electronic Case Report Form (eCRF). Every effort must be made to perform the protocol-specified safety follow-up procedures to capture AEs and serious adverse events (SAEs) for the whole duration of the study. Refer to section 6.1.4

4.5. Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (at least 3 attempts including 1 phone call and 1 written message to the participant) and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

4.6. Premature termination or suspension of study

This study may be temporarily hold or prematurely terminated if there is sufficient reasonable cause.

Section 8.3 describes the study halting rules, specifying the number of adverse events, as well as the nature and/or the severity of events, that would trigger the temporary suspension of the study, pending a safety investigation and potential subsequent premature termination of the study.

Written notification, documenting the reason for study suspension or termination, will be provided to all involved parties.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IEC and CA.

4.7. Definition Start and End of the trial

The start of the trial is defined as the first patient first visit (FPFV) in the trial.

The end of the trial is defined as completion of the last visit of the last patient (LPLV) in the trial.

5. STUDY TREATMENT

5.1. Study treatment and control description

Intervention name	NVDX3
Dose formulation	Vial
Unit dose Weight	4g +/- 0.1g of dry powder
Dosage level(s)	Max 1 unit dose
Route of administration	Implant surgery
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided by Novadip Biosciences
Packaging and labeling	The IMP will be manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and in accordance with all applicable laws or regulations. Each IMP carton will be labeled according to the country requirements. Details of the packaging and labeling will be provided in the "NVDX3-CLN01 IMP Handling Manual"

5.1.1. Formulation, appearance, packaging and labeling

The active ingredient in the NVDX3 drug substance (DS) is a lyophilized powder composed of hydroxyapatite/beta-tricalcium phosphate (HA/TCP) particles embedded in an ECM, biologically active growth factors and non-viable osteogenic cells.

The NVDX3 powder is presented in a vial (primary package) placed in a plastic bag (secondary package), both sterilized by gamma radiation.

5.1.2. Product storage and stability

NVDX3 vial should be stored at room temperature (15-25°C).

[redacted]

The investigator or designee must confirm at receipt of the IMP the intactness of the vial and check that the temperature conditions have been maintained during transit, report any discrepancies and wait for further instructions by the Sponsor before using the IMP. All IMPs must be stored in a secure, controlled, and monitored area in accordance with the storage conditions, with access limited to the investigator and/or authorized site staff.

Any quality concern related to an IMP or temperature exposure must be immediately reported as per "NVDX3Handling Manual".

5.1.3. Preparation

Before use/prior to implantation, the content of the vial must be reconstituted aseptically by the surgeon

5.1.4. Dosing

The total administered quantity of NVDX3 will depend on the bone defect size but cannot exceed the maximum reconstituted implant volume

5.1.5. Route of administration/ applied surgical technique

[redacted]

5.1.6. Duration of therapy trial treatment

NVDX3 is administered during a single surgical intervention.

5.2. IMP accountability

The investigator is responsible for the IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of used/unused records).

The volume of NVDX3 implanted will be estimated during the surgery and by using post-op CT scans.

Refer to the "NVDX3-CLN01 IMP Handling Manual" for complete process description.

5.3. Prohibited medications, treatments, and procedures

Prohibited medications as per exclusion criteria are:

- Chronic, currently ongoing or planned during course of the trial, use of any medications that in the opinion of the investigator might affect bone metabolism or the quality of bone formation such as bisphosphonates, steroids, methotrexate, anticoagulant therapies, immunosuppressant therapy, or immunotherapy.
- The addition of any bone enhancing pharmacological agents (e.g., autogenous recombinant human bone morphogenetic protein-2), bone scaffolds/carriers or autologous bone, in addition to the NVDX3 graft, is not allowed.

6. STUDY SCHEDULE

6.1. Schedule of Activities Table

		Screening	Acute safety FU				Long-term safety FU			Early Termination
		V1	V2 [1]	V3	V4	V5	V6	V7	V8	ETV
					W2	W6	M3	M6	M12	
			Implant Surgery IS (Max 7 days after DRF diagnosis)	Hospital Discharge HD	IS+13d ± 2d	IS+42d ±7d	IS+90d ± 15d	IS+180d ± 30d	IS+360d ± 30d	
Informed consent		×							×[9]	×[9]
Eligibility criteria		×								
Demography		×								
Medical and concomitant medication history		×								
Index fracture evaluation/classification		×								
Physical examination		×	×	×	×	×	×	×	×	×
Weight/Height (BMI)[8]		×	×	×	×	×	×	×	×	×
Triplicate 12-Lead ECG			×						×	
Vital signs		×	×	×	×	×	×	×	×	×
Inspection of the skin of the affected arm[2]		×	×	×	×	×	×	×	×	×
Standard safety laboratory[3]		×		×	×	×	(×)	(×)	(×)	
Serology (HIV, HBV & HBC)		×								
Pregnancy test[4]		×							×	
Implant Surgery (IS)			×[5]							
Peri-operative IS related information			×							
Grip strength test				×	×	×	×	×	×	
NRS-pain		×		×	×	×	×	×	×	
PRWE				×	×	×	×	×	×	
MMWS				×	×	×	×	×	×	
Radiological efficacy[6]	AP/LAT X-ray	×*	×[7]*	×*	×*	×*	×*	x	×	
	DECT-scan	×* (Normal CT)		×			×		×	
AE/SAE collection			×	×	×	×	×	×	×	×
Concomitant medication			×	×	×	×	×	×	×	×
Concomitant therapy				×	×	×	×	×	×	×

1 In-clinic stay: The patient may be hospitalized before the surgery following to hospital standard of care. The required pre-operative assessments can be done up to 3 days before the surgery.
2 Skin inspection to evaluate potential surgical site infections.
3 At screening, Discharge, V4 and V5: safety laboratory analyses are mandatory. At V6, V7 and V8: Upon occurrence or any suspicion of safety related issues.
4 In women of childbearing potential only: a serum pregnancy test will be performed at Screening and at V8
5 Follow the instructions ad per "NVDX3 handling Manual".
6 To guarantee image quality, all X-rays and CT-scan acquisitions will need to strictly follow the imaging instructions as described per "Imaging Acquisition Manual".
7 AP/LAT X-rays: both after insertion of fixation device, and after insertion of the NVDX3 implant (at the end of the surgery)
8 Height at screening only
9 Informed consent proposing participation to the long-term safety follow-up study (NVDX3-CLN0X)
* Standard of care image acquisitions for the diagnosis and follow-up of DRF

6.1.1. Screening visit

- Eligibility check
- Medical history, including diabetes and osteoporosis status
- Target DRF fracture classification according to the Distal Fracture Classification systems (Appendix 1)
- Physical examination: (Refer to section 8.1.1)
- NRS-pain (which will also be used as the reference NRS-pain to which the follow-up patient reported outcomes (PRO) will be compared)

Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the reason for failure has been resolved at the time of rescreening.

Participants who have laboratory values that are marginally outside the defined range(s) for inclusion in the study may have those tests repeated once, if there is realistic chance of normalization having occurred. This should be discussed with the Sponsor Study Physician.

6.1.2. Implant Surgery

- For the standardized surgical technique and ostheosynthesis materials used please refer to section 5.1.5 and 0
- [redacted]
- Record (serious) adverse events as reported by the patient or observed by the investigator (including abnormal radiological observations).
- Record changes in concomitant medication as reported by the patient or prescribed by the investigator

6.1.3. Hospital discharge visit

The timing of the hospital discharge is at the PI's discretion taking into account the patient status. In case of any adverse events leading to hospital prolongation for any medical reason, a SAE should be completed.

This visit is considered as the reference timepoint for the safety and radiological and clinical efficacy (PRO and physician-based assessment) timepoints

6.1.4. (Early) Termination visit

If a patient ends the study prematurely (before 12 month Follow-up visit), either on own decision (withdrawal of IC or for any other reason), by decision of the investigator, for any other reason like lost to FU, or resulting from a halting rule and/or subsequent decision to terminate the study (described in more detail by the Safety Monitoring Plan) this early termination should be reported through the completion of the "End-of study Form" including the following information:

- Date of termination
- Reason for termination
- If lost to follow-up, a formal confirmation of the 3 contact attempts should be documented

6.1.5. Unscheduled visit

Additional visits as per standard of care (e.g., visits with the anesthesiologist before or after the orthopedic surgery, additional safety visit including blood sampling) are not part of the study schedule. Except for the reportable safety events (see safety reporting section for more instructions), non-safety related data generated during those unscheduled visits will not be recorded.

7. EFFICACY ASSESSMENTS AND- PROCEDURES

7.1. Study procedures/evaluations

Consecutive study visits, including clinical efficacy assessments should be conducted by the same clinician, in order to standardize that evaluation and reduce background noise (bias) as far as possible.

The patient-reported outcome (PRO) questionnaires should be completed by the patient in a quiet place prior to any discussion regarding study-related issues, disease status, or treatment effect with the investigator/site staff. The PROs will be completed by the study participant on paper at the site, during study visits. The PROs and physician completed questionnaire should be checked for completeness by the clinical staff.

7.1.1. Grip strength test

Grip strength will be measured by using an hydraulic hand dynamometer with the elbow flexed 90 and the forearm in neutral rotation. Values are expressed as the percentage of the strength on the contralateral (uninjured) side.

7.1.2. Physician reported Modified Mayo Wrist Score

The Modified Mayo Wrist Score (MMWS) is a modification of the Geen and O'Brien score (Appendix 4). There is a total of 100 points which are divided among the evaluator's assessment of pain (25 points), active flexion/extension arc as a percentage of the opposite side (25 points), grip strength as a percentage of the opposite side (25 points), and the ability to return to regular employment or activities (25 points).

Pain is rated as none (25 points), mild (20 points), moderate (10 points), or severe (0 points) by the evaluator, based on the patient's subjective description.

The total score ranges from 0 to 100 points with higher scores indicating a better result. An excellent result is defined as 90–100 points, good is 80–89, fair is 65–79 points, and poor is less than 65 points.

7.1.3. Patient reported Numeric Rating Scale for pain

Numerical rating scales (NRSs) are the simplest and most commonly used scales. The numerical scale is most commonly 0 to 10, with 0 being “no pain” and 10 being “the worst pain imaginable.” The patient draws a circle around the number that best describes the pain dimension, usually intensity. Advantages of NRSs include simplicity, reproducibility, easy comprehensibility, and sensitivity to small changes in pain[35].

For more details, please refer to Appendix 5.

7.1.4. Patient Reported Wrist Evaluation

The PRWE is a 15-item questionnaire designed to measure wrist pain and disability in activities of daily living. The PRWE allows patients to rate their levels of wrist pain and disability from 0 to 10, and consists of 2 subscales:

- Pain subscale: contains 5 items each of which is further rated from 1-10. The maximum score in this section is 50 and minimum 0
- Function subscale: contains total 10 items which are further divided into 2 sections i.e specific activities (having 6 items) and usual activities (having 4 items). The maximum score in this section is 50 and minimum 0.

For more details, please refer to Appendix 6.

7.1.5. Efficacy assessment by the independent central radiologists

Besides bone formation, bone remodeling and bone union will be assessed as described in more detail in the Appendix 8 and/or the “Imaging Reading Manual”.

8. SAFETY ASSESSMENTS AND PROCEDURES

8.1. Specification of safety parameters

8.1.1. Physical examination

A brief physical examination will include the assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen).

- Height and weight will also be measured, Body mass index is to be calculated and recorded.
- Algodystrophy evaluation: Assessment of complex regional pain syndrome using the Budapest criteria
- Skin inspection of the affected arm, in order to evaluate the potential surgical site infections
    - Skin color (Pale/cyanotic/other)
    - Signs of local infection (yes/no)
    - Swelling (oedema) (yes/no)
    - Arm temperature (Normal/cold/hot)

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.1.2. Vital signs

Body temperature, pulse rate, respiratory rate, and BP will be assessed.

BP and pulse measurements will be assessed after 5 minutes of rest in a supine position (in a quiet setting without distractions such as a television or cell phones) with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the eCRF.

8.1.3. Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of Activities

All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

When ECG recording coincides with other, potentially disturbing procedures (such as blood sampling) the ECG should always be performed first, if at all possible.

8.1.4. Clinical laboratory evaluations

Clinical Laboratory will be obtained as outlined in the Schedule of Activities.

List of clinical laboratory tests to be performed are:

- Hematology (Heamoglobin, Heamatocrit, Red blood cells, white blood cells, platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes and erythrocyte sedimentation rate)
- Coagulation (activated partial thromboplastin time, prothrombin time-INR (Quick) (PT-INR), Fibrinogen)
- Biochemistry (NA+, K+, CL-, AST, ALT, AP, GGT, total protein, total bilirubin, CRP, Uric acid, LDH, CK, Glucose, Ca++, Phosphorus, TSH, Vit D)
- Serology (at screening only): HIV, Hepatitis B and C (HBV& HBC)

Blood testing is required up to 6 weeks post-grafting surgery supporting the evaluation of acute toxicity.

However, upon any suspicion of a safety related issue the investigator needs to define, upon his medical judgement, if any required laboratory analysis should be required. All ad-hoc clinically significant out of range laboratory assessments, will be recorded though (S)AE reporting.

The total amount of blood planned to be collected over the duration of the study will be approximately 300cc.

8.1.5. Specimen preparation, handling, and storage

All blood laboratory evaluations will be performed by the local laboratory in accordance with its standard of care preparation (including required blood volumes, the type and number of blood sampling tubes and other blood sampling materials), handling and storage procedures.

All samples will be discarded after analysis and results records

8.1.6. Safety assessment by local radiologist

In order to identify potential safety signals, the local radiologist, at each study visit involving imaging needs to fill the safety questionnaire, as outlined in appendix 7. All potential safety findings need to be entered into the patient file and clinically relevant observations should be recorded though the (S)AE reporting.

8.1.7. Adverse Events and Serious Adverse Events

Definition adverse events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered the NVDX3 therapy and which does not necessarily have to have a causal relationship with this treatment

Events meeting the AE definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., radiological acquisitions, vital signs measurements), including those

that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Principal Investigator (e.g. not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after trial treatment administration even though it may have been present before the start of the trial.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Principal Investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.
- Pregnancy

Definition of serious adverse events (SAE)

A serious adverse event (AE) or suspected adverse event/reaction is any untoward medical occurrence that at any dose, in the view of either the Principal Investigator or the Sponsor, it results in any of the following outcomes:

- **Death**
- **A life-threatening adverse event**

  The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Inpatient hospitalization or prolongation of existing hospitalization**

  In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g., respite care, the fact that there is no-one at home to care for the patient).

- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **A congenital anomaly/birth defect**

- Any **medically significant events** that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical treatment to prevent one of the outcomes listed in this definition.

  Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Treatment Emergent AEs

A Treatment-emergent adverse event (TEAE) is defined as an event that emerges after the NVDX3 was implanted, having been absent pre-implant surgery, or worsens relative to the pre-implant state.

AE of Special Interest (AESI)
The following adverse events will be considered as of special interest:

- Hypersensitivity reaction
- Immunological reaction
- An AE requiring immunosuppressive medication
- Ectopic bone formation
- Tumor formation
- Treatment failure:
    - Continued non-union/Non-fusion
    - Refracture of the targeted area
    - Revision surgery/intervention including removal of NVD-X3
    - Any other condition considered by the treating physician as treatment failure

Reportable AESI
An AESI that is assessed by the PI as possibly, probably or definitely related to NVDX3 is defined as a reportable AESI (rAESI) and will be evaluated throughout the same process as a SAE (see section 8.2.5)

AE classification

a) <u>Severity of the AE</u>

Severity of adverse events (AEs) is assessed as follows:

- **Grade 1 - Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 - Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- **Grade 3 - Severe or medically significant but not immediately life-threatening**; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4 - Life-threatening consequences**; urgent intervention indicated.
- **Grade 5 - Death related to AE**.

b) Relationship to the NVDX3 treatment

All adverse events (AEs) must have their relationship to the NVDX3 treatment (relatedness to the NVDX3 implant, the NVDX3 implant procedure and other study or non-study related procedures) assessed by the Principal Investigator who examines and evaluates the patient based on the Investigator Brochure, the temporal relationship of the event and his/her clinical judgment. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors will be considered and investigated. The degree of certainty about causality will be graded using the categories below.

For each AE/SAE, the Principal Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Principal Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Principal Investigator always assesses the causality for every event before the initial transmission of the SAE data to the Sponsor. The Principal Investigator may change in the eCRF his/her opinion of causality in light of follow-up information: a SAE follow-up report with the updated causality assessment will be recorded in the eCRF.

As part of medical review, the causal relationship will also be assessed by the safety officer of the Sponsor or his delegate.

c) Expectedness

An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for NVDX3. The 'expectedness' of a serious adverse reaction (SAR) is assessed in the light of the reference safety information (RSI) included in the latest version of the approved Investigator Brochure.

8.2. Safety Reporting procedures

8.2.1. Time period and frequency for collecting AE/SAE information

All AEs and SAEs will be collected from the signing of the ICF until the (early) Termination Visit at the time points specified in the Schedule of Activities (Section 6.1).

Any medical condition that is present at the time of the patient's screening will be considered as baseline and not reported as an AE. However, if the trial patient's condition deteriorates at any time during the trial, it will be recorded as an AE.

Changes in the severity of an AE/SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Investigators are not obliged to actively seek AE or SAE in patients after their final discharge from the study. However, if the Principal Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to NVDX3 or trial participation, the Principal Investigator must promptly notify the Sponsor or designee.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IMP under clinical investigation are met.

8.2.2. Detection of AE/SAE information

AEs and SAEs may come to the attention of trial personnel during trial visits and interviews of the patient, his/her parent(s) and/or legal guardian(s) presenting for medical care, or upon review by a trial monitor.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.2.3. Follow-up of AE/SAE information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All SAEs, and non-serious related AEs (excluding unlike related events) will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up.

8.2.4. Adverse Event reporting

When an AE occurs, the Principal Investigator, or defined delegate(s), will review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event and record all relevant AE information in the eCRF.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the case report form (eCRF) within 5 working days of event awareness.

Information to be collected includes event description, time of onset, investigator's assessment of severity, relationship to surgical procedures and trial product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

AEs occurring while on trial must be documented appropriately regardless of relationship.

8.2.5. Serious Adverse Event and reportable AESI reporting

The Principal Investigator is responsible to report to the Sponsor, all SAEs and reportable AESI (rAESI) within 24 hours after obtaining knowledge of the event, whether or not considered trial treatment related.

SAE and rAESI will be reported electronically through completion of the electronic safety form (eCRF).

> Note: An Initial notification via telephone does not replace the need for the investigator to complete and sign the safety CRF pages

Other supporting documentation of the event may be requested by the Sponsor or designee and should be provided as soon as possible. Hospital or patient records, attached to the safety form, need to be anonymized and proper identification (patient number) needs to replace the identifiers.

All SAEs/rAESIs and updated SAE/rAESI data will be recorded and reported to the Sponsor, or designee, within 24 hours after obtaining knowledge of the event or updated information

After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site staff receives information about a new safety from a trial patient or receives updated data on a previously reported SAE /rAESI after the electronic data collection tool has been taken off-line, the site can report this information to the Sponsor or designee on a paper safety form.

8.3. Study Halting rules

As a consequent to the nature of the product, implanted through a single administration surgical intervention, study halting rules will **only be applicable during the period between the first patient implant and last patient implant surgery visit. After completion of the last implant surgery, no more new patients will be added, and all implanted patients will need to be followed for safety for the whole study period.**

During this period, important safety events resulting from any study procedure, including NVDX3 implant surgery, may temporarily suspend or prematurely terminate any planned surgical interventions or new study enrolment.

Written notification, documenting the reason for trial suspension or termination, will be provided by the suspending, or terminating party to investigators, the Sponsor and regulatory authorities. Halting the study will allow time to review the safety concerns with CA/IEC and consider if is possible to construct a path forward. Trial may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IEC and/or regulatory authorities.

If the trial is prematurely terminated or suspended, the Principal Investigator will promptly inform the patients, the IEC, and the Sponsor will provide the reason(s) for the termination or suspension to the regulatory authorities. The parent(s) or the legal guardian(s) of the patient will be contacted, as applicable, and be informed of changes to trial visit schedule.

If an event, corresponding to the above-mentioned study halting rules, occurs beyond the above-mentioned period the study will not be halted as all 10 recruited patients have been implanted with NVDX3 and continued safety surveillance must be guaranteed. All concerned parties will be notified promptly in accordance with the drug safety reporting requirements, allowing proper review evaluation of the events and eventually decide on the path forward in the best interest of the patient.

8.4. Safety Oversight

A detailed overview of the roles and responsibilities, the safety process and timelines are detailed in the “Safety Monitoring Plan”.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical and analytical plans

A Statistical Analysis Plan (SAP) will be prepared to precisely define the final statistical analysis of the data. The SAP will be based on the study protocol and will be in compliance with ICH E9.

9.2. Statistical Hypothesis

Only descriptive statistics will be used.

9.3. Analysis Datasets

A Safety Set will include all patients treated with study medication.

An Efficacy Set will include patients satisfying all inclusion criteria and none of the exclusion criteria and for whom any efficacy assessment is available.

9.4. Description of statistical methods

9.4.1. General Approach

Descriptive statistics will be used throughout all the analyses.

Continuous variables will be summarized using the mean, standard deviation, median, and range.

Categorical variables will be summarized using frequency counts and percentages.

9.4.2. Analysis of the (primary) safety endpoint(s)

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The frequency, causal relationship, expectedness and severity of AEs and SAEs will be summarized for the overall study period and for the following treatment phases:

- Acute phase: IS till 6 weeks post-IS (V5 included)
- Long term phase: beyond 6 weeks post-IS (V5 excluded) till study completion (completion V8 or early termination whichever comes first)

Besides a listing including all SAEs and NVDX3 related AEs occurring between screening (V1) and 12-months post-IS (Primary endpoint) tables will be generated for:

- All TEAEs and SAEs summarized by System Organ Class (SOC) and Preferred Term (PT)
- All related TEAEs and SAEs (according to the Principal Investigator) summarized by SOC and PT
- All related TEAEs and SAEs (according to the sponsor) summarized by SOC and PT
- All TEAEs and SAEs summarized by SOC, PT, and highest severity
- All unexpected SAEs summarized by SOC and PT

- All AESIs and rAESIs summarized by SOC and PT

More details on the descriptive tables will be given in the SAP.

9.4.3. Analysis of the secondary endpoint(s)

The analysis of secondary endpoints will be described in the SAP (same for exploratory endpoints)

9.4.4. Analysis of the exploratory endpoint(s)

[redacted]

9.4.5. Baseline and follow-up descriptive statistics

Descriptive baseline characteristics will be listed.

Concomitant medications will be tabulated and listed by International Nonproprietary Names (INN). Additionally, pain medication will also be listed separately in view of its importance for the clinical outcomes.

9.4.6. Planned interim analyses

Safety and efficacy analysis might be performed as needed on a patient-by-patient level. Interim descriptive study analysis can be initiated to support safety, scientific and regulatory needs at any time

9.4.7. Tabulation of individual response data

Individual patient data listings will be produced in accordance with ICH/E3 guidelines.

9.5. Sample size

No formal sample size calculation has been performed for this study since no formal hypothesis will have to be tested. However, as this is an early phase Proof of Concept study, the number of patients was limited to 10 individuals[36].

9.6. Measures to minimize bias

To minimize bias, some potential variables have been standardized:

- Centralized Image Reading
- Maximum 2 sites, one orthopeadic surgeon per site performing the intervention (limit large inter-site and inter-surgeon variabilities)
- Implant surgery:
  - The applied surgical technique and type of osteosynthesis devices has been standardized
  - Maximum volume of NVDX3 is fixed

10. CLINICAL MONITORING

Site monitoring is conducted to ensure that the rights and well-being of trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH E6 GCP current version including GCP for ATMPs and with applicable regulatory requirement(s).

The Sponsor's monitor or representative is responsible for the eCRF review at regular intervals throughout the trial to ensure adherence to the protocol and all applicable regulations on the conduct of clinical research. The monitor should have access to patients' medical records and any other study -related records needed to verify the entries in the eCRF.

The investigator(s)/institution(s) will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s), providing direct access to source data/documents.

It is important that the Principal Investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process. The Principal Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

Details of site monitoring are documented in a Trial Monitoring Plan (TMP). The TMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the TMP.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time, including any copies of transcriptions that are certified as per GCP definition after verification as being accurate and complete.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the timeliness of the data reported and ensuring that the source data are attributable, legible, contemporaneous, original, accurate, and complete (ALCOAC principles) to ensure accurate interpretation of data. The Principal Investigator must list the location and the responsible person for the collection of the source data that will be used for data entry in the eCRF. This list must be signed and dated by the Principal Investigator before the start of the screening period.

If required, in order to support the sites, hardcopies of the trial visit worksheets may be developed by the site for use as source document worksheets for recording data for each patient enrolled in the trial if not collected in the medical file. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

The following data are source data in addition to the regular patient's medical file:

- Signed informed consent form (ICF)
- Printouts of electronic devices
- Laboratory reports
- Study logs

The scope of the Source Data Verification (SDV) is regulated in the Trial Monitoring Plan set up for this clinical trial. Source documents that are required to verify the validity and completeness of data entered in the eCRFs must not be obliterated or destroyed.

The electronic clinical data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Use of a site electronic system

When clinical observations are entered directly into a site's computerized medical record system (e.g. in lieu of original hardcopy records, which is not the Sponsor's eCRF), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

PI should provide adequate documented evidence on the validation process for electronic computerized systems used at hospital.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor is committed to ensure internal quality management of trial conduct, data and biological specimen collection, documentation and completion in accordance with the Quality Management System.

Quality Control (QC)

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated (including radiological image acquisitions) and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, with ICH E6 GCP current version including GCP for ATMPs and with applicable regulatory requirement(s).

The site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

In addition, an individualized quality management plan is developed for each Service Provider contracted by the Sponsor for the management of the trial.

Quality Assurance (QA)

ICH E6 GCP guidelines state that independent audits and inspections of clinical trials should be performed based on risk assessment. It is the responsibility of the Principal Investigator and trial staff to ensure all trial related documentation is filed accurately and to make this available to the Sponsor or designee, regulatory agencies, providing direct access to source data/documents.

On-Site Audits

In accordance with ICH E6 GCP and the Sponsor or designee's audit plans, this trial may be selected for an audit. Inspection of site facilities (e.g. drug storage areas, laboratories) and review of trial related records may occur in order to evaluate the trial conduct and compliance with the protocol, ICH E6 GCP, and applicable regulatory requirements.

The Principal Investigator will permit an independent audit by an auditor mandated by the Sponsor, after reasonable notice. An audit or a regulatory inspection is intended to determine if the trial was conducted as per protocol, ICH E6 GCP, and applicable regulatory requirements; if the rights and well-being of the patients were protected; and if the data relevant for the evaluation of the Investigational Medicinal Product (IMP) were captured, processed and reported in compliance with the planned arrangements.

Regulatory authorities may perform an inspection of the trial until several years after its completion. As for an audit, the Principal Investigator will permit a direct access to all trial documents, IMP accountability records, source records, and source data. If an inspection is announced, the Sponsor must be informed without delay (by addressing this occurrence to [redacted]).

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in with ICH E6 GCP current version including GCP for ATMPs and with applicable regulatory requirement(s).

13.2. Ethics Committee

This study is performed in Luxemburg only

This clinical study is conducted after review and approval by the competent Luxembourg authority (Luxembourg Ministry of Health), and favorable opinion from the National Research Ethics Committee (CNER).

The protocol, informed consent form(s), and all patient materials will be submitted to the IEC for review and favorable opinion

Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval before the changes are implemented to the study. All changes to the consent form will be approved; a determination will be made regarding whether previously consented patients need to be re-consented.

13.3. Informed consent process

The Informed Consent Form (ICF) will include consent to participate in trial procedures, including all the surgical interventions (IS) as defined by ICH E6 GCP and applicable regulatory requirements.

Prior to the start of the study at a site, the Principal Investigator must have obtained the IEC written approval/favorable opinion on the written ICF and on any other written information to be provided to the patient

The written approval of the IEC together with the approved ICF must be filed in the study files and a copy of these documents must also be provided to the Sponsor.

Obtaining informed consent is a process that is initiated prior to the participation of the patient in the trial and continues throughout the patient's trial participation.

The Principal Investigator or his/her delegate will explain the research purpose of the trial to the patient or its legal guardian(s) and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient/legal guardian(s)'s comprehension of the purposes, procedures, and potential risks of the trial and of the rights of the study participant.

The patients or the legal representative(s) will have the opportunity to carefully review the ICF and can ask questions prior to confirming patient's participation. The patient, if appropriate, and/or the legal representative(s) should have the opportunity to discuss the trial with their family or surrogates or think about it prior to agreeing to participate.

The patient or the representative(s) will sign the ICF prior to any trial related procedures being started. The ICF is signed by the Principal Investigator or his representative.

The patient or the representative(s) must be informed that participation is voluntary and that he may withdraw from the trial at any time,without any need for justification and without prejudice.

In addition, the patient and/or the representative(s) have to authorize in writing that the patient's source records may be reviewed by third parties, such as a Sponsor representative, an auditor, or a regulatory inspector in accordance with applicable regulatory requirements.

The ICF and any accompanied document (in accordance with regulations specified under section 12.4) has to describe in detail how and to whom and for what purpose the personal data will be transmitted.

A copy of the signed ICF will be given to the patient or the representative(s) for their records.

The informed consent process will be documented in the source document (including the consent), and the form(s) signed before the patient undergoes any trial-specific procedures.

The rights and welfare of the patient will be protected by emphasizing that the quality of the patient's medical care will not be adversely affected if the patient or the legal guardian(s) decline to participate in this trial.

13.4. Patient and data confidentiality

Data Protection

Sponsor staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to the Sponsor (or designee) will be identified only by the participant number assigned at Screening.

The investigator agrees that representatives of the Sponsor, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with GDPR and all applicable privacy laws. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities/Data protection authorities.

Patient personal data

Patient's research data shall be adequate, relevant, and not excessive in relation to the purposes for which they are processed.

The processing[4] of the personal data for scientific research purposes is subject to appropriate safeguards according to national/regional patient data protection legislations.

As concerns the patient's identification in the eCRF:

Each patient will be identified in the clinical trial records by a unique trial identification number that includes several letters and digits, representing the screening number. The digits will not contain any number that could indirectly identify the patient such as his/her medical dossier number, social security number, etc. The initials of the patient will not be collected in the clinical trial records.

The partial birth date (limited to month and year) will be collected in the clinical trial records to determine the approximate age of the patient.

Sponsor's responsibilities

The Sponsor shall comply with all relevant national/regional patient data protection requirements laid applicable legislations, including GDPR in EU.

Through the Informed Consent Form, the Sponsor shall inform (legal representatives of) the patients in the trial about their privacy rights to understand and control how their health information is used and shared, including rights to examine and obtain a copy of their health records as well as to request corrections.

The Sponsor may transfer patient's research data to a third country or an international organization in accordance with applicable legislation where the patients are enrolled. No information concerning the trial, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

Investigators and research staff's responsibilities

Patient confidentiality and privacy are strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover all testing of biological samples in addition to the clinical information relating to patients. Therefore, the trial protocol, documentation, data, and all other information generated will be held in strict confidence by the site trial team.

To comply with the national/regional patient data protection legislations, the Investigators and research staff undertake to:

- Inform the parent(s) or the legal guardian(s) and the patient him/herself if applicable (age based) about his/her data protection rights and retain evidence of communication thereof.
- Provide the parent(s) or the legal guardian(s) and the patient him/herself if applicable (age based) with evidence of communication when such evidence are requested either by the Sponsor and/or any legitimate authority.
- Apply pseudonymization of patient's research data prior to transmitting data as defined by the Sponsor.

[4] Processing patient's research data concerns any operation that affects the data from a clinical trial during its entire life cycle, from its collection by the sites as source data to its reporting, archival and destruction.

- Maintain all documents and records including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this trial which may be subject to review by the trial monitor, other authorized representatives of the Sponsor, representatives of the IEC and regulatory agencies. The site will permit access to such records.
- Store securely the trial patient's contact information for internal use during the trial. At the end of the trial, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IEC, Institutional policies, Sponsor requirements or the applicable law.
- Notify the defined Sponsor's contact (specified in a mutual Site Agreement) about
  - any research data protection issue or breach upon awareness
  - any patient's request to exercise his/her rights on research data
- Notifying the concerned patient(s) as per local site's data protection procedure about research data protection breach, whenever confirmed by the Sponsor.

13.5. Future use of stored specimens

- All blood samples are analyzed by the investigational site facilities and will not be stored. The overage (residuals) of IMP NVDX3 not being used during the surgery of the patient must be destroyed at the site according to local destruction procedure.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data collection and management responsibilities

Data collected for this trial will be analyzed and stored at the Service Provider(s) designated by the Sponsor. After the trial is completed, the pseudonymized data will be transmitted to and stored at the Sponsor. Information about collected and transmitted data will be included in the Information for patients/parents/Legal guardians regarding the processing of the patient's personal data.

14.2. Study records retention

Trial documents should be retained for 30 years after the closure of the trial according to the Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products (C(2019) 7140 final) (ATMPs - EU specific terminology for, among others, stem cell therapy) dated 10-Oct-2019.

No records will be destroyed without the written consent of the Sponsor, if applicable. After the required retention period has expired, the site shall provide the Sponsor with a written notice at the latest 60 calendar days before destroying any of the Trial Deliverables, or in accordance with the site clinical trial agreement. The Sponsor will notify the Principal Investigator or the site when any records may be discarded.

14.3. Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH E6 GCP, Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products (C(2019) 7140 final) or applicable regulatory requirements. The noncompliance may be either on the part of the patient, the investigator, or the site staff. As a result of deviations, a root cause analysis needs to be performed and a corrective and preventive actions are to be developed by the site and implemented promptly.

These practices are consistent with the following sections of the ICH GCP E6 guidelines:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 1 working day of identification of the protocol deviation. All deviations must be addressed in trial source documents.

Protocol deviations (including deviations that might introduce additional patients safety risks) must be sent to the reviewing Independent Ethics Committee (IEC) and Luxemburg Ministry of Health as per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IEC requirements.

Further details about the handling of protocol deviations will be included in the Protocol Deviation Plan. The list of deviations will be provided to the site on an ongoing basis.

14.4. Publication and data sharing policy

This trial will be conducted in accordance with the following publication and data sharing policies and regulations:

All the relevant data and information will be reported in a Clinical Study Report (CSR) on safety and efficacy data of the trial, of all enrolled patients.

[redacted]

15. SERVICE PROVIDER MANAGEMENT

The Sponsor will work in collaboration with different service providers supporting data and safety management (including statistics, medical writing, central image reading), medical and site monitoring. A service providers log, including names, contact details and responsibilities, is maintained and available in the clinical study documentation (available in the investigator site file and trial master file).

16. CONFLICT OF INTEREST POLICY

The independence of this trial from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the trial and for 1 year after completion of the trial.

The Sponsor has established policies and procedures for all trial group members to disclose all conflicts of interest and established a mechanism for the management of all reported dualities of interest.

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APPENDICES

APPENDIX 1: Distal Radius Fracture Classification systems

AO/OTA Classification of Fractures and Dislocations:	
23A	**Extraarticular Fracture**
23A1	Ulna fractured; radius intact
23A2	Radius, simple and impacted
23A3	Radius, multifragmentary
23B	**Partial articular fracture of radius**
23B1	Sagittal
23B2	Coronal, dorsal rim
23B3	Coronal, palmar rim
23C	**Complete articular fracture of radius**
23C1	Articular simple, metaphyseal simple
23C2	Articular simple, metaphyseal multifragmentary
23C3	Articular multifragmentary

Frykman - Fracture		
Fractures	Distal ulna fracture present	Distal Ulna fracture absent
Extra-Articular	I	II
Intra-articular		
• Radio-Carpal joint involved	III	IV
• Radio-Ulnar joint involved	V	VI
• Radio-Carpal and Radio-Ulnar involved	VII	VIII

Melone's - intra-articular	
Fracture	Description
Type I	Four components (radial shaft, radial styloid, dorsal medial and volar medial fragment) are undisplaced or show variable displacement of the medial complex as a unit. Such fractures show minimal comminution and are stable after closed reduction.
Type II	There is significant displacement of the medial complex as a unit with a communition of radial metaphysis and instability (the punch fracture)
Type III	Displacement and instability are similar to type II, with the spike fragment of the radial shaft often projection into the flexor compartment (spike fractures)
Type IV	There is severe disruption of the radial articular surface and the dorsal and volar medial fragments show wide separation or rotation. There are extensive soft tissue damage and nerve injury
Type V	Fracture results from a severe force comprising both compression and crush that cause extensive comminution, often extending from the articular surface of the diaphysis

Fernandez - distal end	
Bending	Metaphysis fails due to tensile stress (Colles' and Smith fracture)

Compression	Fracture of the surface of the joint with impaction of subchondral and metaphyseal bone (the punch fracture)
Shearing	Fracture of surface of the joint (Barton fracture and fracture of radial styloid process)
Avulsion	Fracture of ligamentous attachments (fracture of ulnar and radial styloid process)
Combination	Combination of (1) – (4) and high velocity injury

APPENDIX 2: Use of Dual Energy CT [37]

Conventional or single energy CT (SECT) utilizes a single polychromatic X-ray beam (ranging from 70 to 140 kVp with a standard of 120 kVp) emitted from a single source and received by a single detector. The inherent contrast of the image dataset generated by this process depends on differences in photon attenuation of the various materials that constitute the human body (ie, soft tissue, air, calcium, fat). The degree that a material will attenuate the X-ray beam is dependent on (1) tissue composition and (2) photon energy level and how closely it exceeds the k-edge (ie, inner electron shell binding energy) of the material. Therefore, tissue attenuation can be manipulated by changing photon energy levels. In DECT, two energy levels (typically 80 and 140 kVp) are used to acquire images that can be processed to generate additional datasets allowing:

- **To reduce metal artifacts (induced by envisioned internal fixation devices)**

  With dual-energy CT, creation of virtual monochromatic images at different kilovolt peak (photon energy) settings allow to freely select the optimal energy for maximum diagnostic image utility (usually between 40 and 140 keV). Researchers have evaluated the quality of virtual monochromatic images at different energy levels in several studies. Metal-artifact reduction with DECT has been extensively studies with all types of scanners Optimal keV level varies but is generally found to be effective between 100 and 160 keV [38,39].

- **To reduce beam hardening artifacts and improved CT-value stability**

  Like any x-ray spectrum, the CT beam is composed of photons with a wide range of energies, with maximum energy expressed as the peak voltage (kilovolt peak, kVp).

  Beam hardening occurs due to a shift of the energy spectrum toward higher energies: when traveling through a material, the low-energy photons of the polychromatic x-ray beams are preferentially attenuated, whereas the high-energy photons are not attenuated as easily. This will cause a shift of the CT-values (Hounsfield Units, HU) to lower numbers due to the fact that they are energy dependent: they represent the degree to which the X-ray intensity is reduced by the tissue. This effect will be amplified in the presence of metallic implants due to increased absorption of low energy photons. There are two important consequences of beam hardening for this study: firstly, the presence of dark bands in the vicinity of the metallic implant which can impair radiological evaluation (qualitatively), secondly a shift in HU values of the tissues which potentially impairs any reliable quantitative assessment of tissue density [39].

- [redacted]

APPENDIX 3: Specifications Carbofix Distal Volar Radius plates and screws

[redacted]

[redacted]

[redacted]

[redacted]

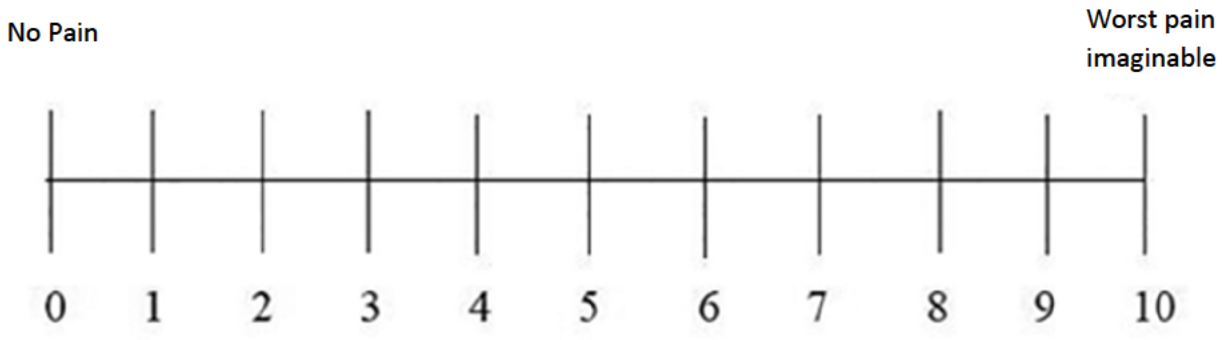
[redacted]

APPENDIX 4: Modified Mayo Wrist Score (MMWS)

Category	Score	Findings
Pain (25 points)	25	No pain
	20	Mild pain with vigorous activities
	20	Pain only with weather changes
	15	Moderate pain with vigorous activities
	10	Mild pain with activities of daily living
	5	Moderate pain with activities of daily living
	0	Pain at rest
Satisfaction (25 points)	25	Very satisfied
	20	Moderately satisfied
	10	No satisfied, but working
	0	No satisfied, unable to work
Range of motion (25 points)	25	100% percentage of normal
	15	75% - 99% percentage of normal
	10	50% - 74% percentage of normal
	5	25% - 49% percentage of normal
	0	0% - 24% percentage of normal
Grip strength (25 points)	25	100% percentage of normal
	15	75% - 99% percentage of normal
	10	50% - 74% percentage of normal
	5	25% - 49% percentage of normal
	0	0% - 24% percentage of normal
Final result (total points)	90 - 100	Excellent
	80 - 89	Good
	65 - 79	Fair
	<65	Poor

APPENDIX 5: Numerical Rating Scale for Pain

Numerical rating scales (NRSs) are the simplest and most commonly used scales. The numerical scale is most commonly 0 to 10, with 0 being "no pain" and 10 being "the worst pain imaginable." The patient draws a circle around the number that best describes the pain dimension, usually intensity. Advantages of NRSs include simplicity, reproducibility, easy comprehensibility, and sensitivity to small changes in pain[35].



APPENDIX 6: Patient-Rated Wrist Evaluation

There are 3 steps to score PRWE

Step 1: Measure the pain score of all 5 items

1. PAIN											
Rate the **average** amount of pain in your wrist over the past week by circling the number that best describes your pain on a scale from 0-10. A zero **(0)** means that you **did not** have any pain and a **ten (10)** means that you had the **worst pain you have ever experienced** or that **you could not do the activity because of pain.**											
RATE YOUR PAIN: Sample Scale ☞	0 No Pain	1	2	3	4	5	6	7	8	9	10 Worst Ever
At rest	0	1	2	3	4	5	6	7	8	9	10
When doing a task with a repeated wrist movement	0	1	2	3	4	5	6	7	8	9	10
When lifting a heavy object	0	1	2	3	4	5	6	7	8	9	10
When it is at its worst	0	1	2	3	4	5	6	7	8	9	10
How often do you have pain?	0 Never	1	2	3	4	5	6	7	8	9	10 Always

Step 2: Measure the function score of all the 10 items and divide it by 2

2. FUNCTION											
A. SPECIFIC ACTIVITIES *Rate the **amount of difficulty** you experienced performing each of the items listed below - over the past week, by circling the number that describes your difficulty on a scale of 0-10. A **zero** (0) means you did not experience any difficulty and a **ten** (10) means it was so difficult you were unable to do it at all.* Sample scale →	0 No Difficulty	1	2	3	4	5	6	7	8	9	10 Unable To Do
Turn a door knob using my affected hand	0	1	2	3	4	5	6	7	8	9	10
Cut meat using a knife in my affected hand	0	1	2	3	4	5	6	7	8	9	10
Fasten buttons on my shirt	0	1	2	3	4	5	6	7	8	9	10
Use my affected hand to push up from a chair	0	1	2	3	4	5	6	7	8	9	10
Carry a 10lb object in my affected hand	0	1	2	3	4	5	6	7	8	9	10
Use bathroom tissue with my affected hand	0	1	2	3	4	5	6	7	8	9	10
B. USUAL ACTIVITIES *Rate the **amount of difficulty** you experienced performing your **usual** activities in each of the areas listed below, over the past week, by circling the number that best describes your difficulty on a scale of 0-10. By "usual activities", we mean the activities you performed **before** you started having a problem with your wrist. A **zero** (0) means that you did not experience any difficulty and a **ten** (10) means it was so difficult you were unable to do any of your usual activities.*											
Personal care activities (dressing, washing)	0	1	2	3	4	5	6	7	8	9	10
Household work (cleaning, maintenance)	0	1	2	3	4	5	6	7	8	9	10
Work (your job or usual everyday work)	0	1	2	3	4	5	6	7	8	9	10
Recreational activities	0	1	2	3	4	5	6	7	8	9	10

Step 3: Add pain and function score.
Total Score = Sum of pain+ function scores (Best Score = 0, Worst Score = 100)
Less score = better outcome

APPENDIX 7: Safety assessments by local radiologist

[redacted]

APPENDIX 8: Extended Lane and Sandhu Scoring tool

Evaluation of bone healing efficacy parameters (including bone formation, bone remodeling and bone union or non-union) will be based on the extended Lane and Sandhu Scoring.

When the surgical treatment incorporates radiopaque material, such as HA/βTCP, bone healing assessment becomes more complex and definition of bone to material separation may not be evident. Simplistic approaches may lose the healing progression, particularly in early evaluations.

The available scoring systems to clinically evaluate fracture consolidation encounter difficulties to interpret progression towards consolidation in long-bone non-union, particularly when incorporating biomaterials in the surgical treatment[43].

During the development of the Sponsors second-generation implant, NVD-003, a radiographic evaluation tool was developed, quantifying the level of bone formation, bone union and bone remodeling obtained after graft implant. The extended Lane and Sandhu Scoring scale (eLSS), developed starting from the validated LSS[44,45], evaluates different parameters against the baseline radiological status; (1) bone formation, defined as filling of the longitudinal gap, (2) bone remodeling, defined as evidence of remodeling of the intramedullary canal and/or cortex and (3) bone union, defined as the filling of the transverse gap. Using CT or radiographic images, this scoring tool e has shown to provide a consistent outcome when used in independent parallel reading parallel follow-up time for long bone nonunion fractures, with a biomaterial included in the surgical treatment.

Extended Lane and Sandhu Scoring (eLSS) scale

Radiographic criteria	
Bone Formation	Distal radius
complete longitudinal defect	0
up to 25% of the longitudinal gap filled against the baseline	1
up to 50% of the longitudinal gap filled against the baseline	2
up to 75% of the longitudinal gap filled against the baseline	3
up to 100% of the longitudinal gap filled against the baseline	4
100% of the longitudinal gap filled against the baseline.	5
Bone remodeling	
no evidence of remodeling against the baseline	0
possible remodeling of intramedullary canal	1
full remodeling of the intramedullary canal and cortex	2
Bone Union	
complete transverse defect	0
up to 25% of the transverse gap filled against the baseline	1
up to 50% of the transverse gap filled against the baseline	2
up to 75% of the transverse gap filled against the baseline	3
up to 100% of the transverse gap filled against the baseline	4
100% transverse gap filled - complete absence of a fracture line.	5
Total LSS score per region	
Min-max	0-12