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SPONSOR'S AGREEMENT WITH PROTOCOL

Study code: NFX88-2A-2018

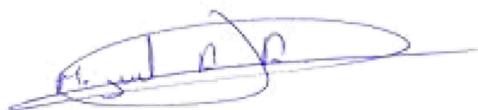
Protocol title:

A randomized, double-blind, placebo controlled, parallel group, multicentric, phase IIa clinical trial to evaluate the safety, tolerability and therapeutic efficacy of daily oral treatment with NFX88 on neuropathic pain in patients with spinal cord injury.

Version:

1, dated 28-Dec-2018

I have carefully read, reviewed and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, such as, among others, the International Conference on Harmonisation Guideline for GCP and the ethical principles that have their origins in the Declaration of Helsinki and agrees in writing to the strict observance of the Law on the Protection of personal data.



Signature

01/02/2019

Date (DD/MMM/YYYY)

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STUDY MEDICAL COORDINATOR AGREEMENT WITH PROTOCOL

Study code: NFX88-2A-2018

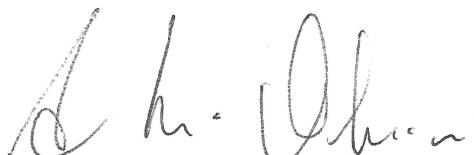
Protocol title: A randomized, double-blind, placebo controlled, parallel group, multicentric, phase IIa clinical trial to evaluate the safety, tolerability and therapeutic efficacy of daily oral treatment with NFX88 on neuropathic pain in patients with spinal cord injury.

Version: 1, dated 28-Dec-2018

I have carefully read and reviewed the study protocol. After reading and understanding the requirements and conditions of the study protocol, I agree to conduct the clinical study according to the international GCP principles, the requirements of the regulatory authorities for verification of source documents and study audit/inspection and the ethical principles that have their origins in the Declaration of Helsinki and agrees in writing to the strict observance of the Law on the Protection of personal data.

I agree to use the study material and to follow the described procedures only as specified in the protocol.

My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties.



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Study code: NFX88-2A-2018

Protocol title: A randomized, double-blind, placebo controlled, parallel group, multicentric, phase IIa clinical trial to evaluate the safety, tolerability and therapeutic efficacy of daily oral treatment with NFX88 on neuropathic pain in patients with spinal cord injury.

Version: 1, dated 28-Dec-2018

I have carefully read and reviewed the study protocol. After reading and understanding the requirements and conditions of the study protocol, I agree to conduct the clinical study according to the international GCP principles, the requirements of the regulatory authorities for verification of source documents and study audit/inspection and the ethical principles that have their origins in the Declaration of Helsinki and agrees in writing to the strict observance of the Law on the Protection of personal data.

I agree to use the study material and to follow the described procedures only as specified in the protocol.

My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties.

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LIST OF ABBREVIATIONS

2OHOA	2-Hydroxy-9-cis-Octadecenoic Acid, 2-hydroxyoleic acid
AE	Adverse Event
AEMPS	Agencia Española del Medicamento y Productos Sanitarios (Spanish Medicines Agency and Medical Devices)
Ag/Ab	Antigen/Antibody
AIS	ASIA Impairment Scale
ALT/SGPT	Alanine Aminotransferase
APP	Electronic Application
ANOVA	Analysis of Variance
A-OA	Albumin-Oleic Acid
A-2OHOA	Albumin-2-hydroxyoleic acid
AIS	Abbreviated Injury Scale
ASIA	American Spinal Injury Association
AST/SGOT	Aspartate Aminotransferase
AUC	Area Under the Curve
BBB	Blood Brain Barrier
b.i.d./b.d.	"bis in die" from Latin, means twice a day, twice daily
ca.	"circa" from Latin, means around, about, approximately
CK	Creatine Kinase
C _{max}	Maximum plasma concentration
CNS	Central Nervous System
CRO	Contract Research Organization
CRF/eCRF	Case Report Form/electronic CRF
CYP450	Cytochrome P450
DLT	Dose Limiting Toxicity
DM	Data Manager
DSUR	Development Safety Update Report
e.g.	"exemplia gratia" from Latin, means for example, example given
ECG	Electrocardiogram

EoS	End of Treatment
EoT	End of Study
ESR	Erythrocyte Sedimentation Rate
FU	Follow-up
g	Grams
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
h	Hour
Hb	Hemoglobin
HCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
hERG	human Ether-à-go-go-Related Gene
IASP	International Association for the Study of Pain
i.e.	“id est” from Latin, means that is
i.t.	Intra thecal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
kg	Kilogram
L	Litter
MAS	Modified Ashworth Scale
MCV	Mean Corpuscular Volume
mg	Milligram(s)
min	Minute
mL	Millilitres
MLD	Minimum Lethal Dose

MNLD	Maximum Non-Lethal Dose
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse Effect Level.
OA	Oleic acid
PD	Progressive disease
PD-Q	PainDETECT Questionnaire
p.o.	“per oral” from Latin, means oral route
PGIC	Patient’s Global Impression of Change
QC	Quality Control
SAE	Serious Adverse Event
SC	Steering Committee
SCI	Spinal Cord Injury
SF	Screening Failure
SOP	Standard Operating Procedure
TCA	When Trichloroacetic Acid
T _{max}	Time to reach peak plasma concentration
t.i.d./t.d.s.	“ter in die”/ “ter die sumendum” from Latin, means three times a day)
VAS	Visual Analogue Scale
Verbatim	“verba/uerba” from Latin, means using exactly the same words as were originally used.
WV	Withdrawal Visit

PROTOCOL SYNOPSIS

Protocol code	NFX88-2A-2018
Protocol version	Version 1, 28th December 2018
Title	A randomized, double-blind, placebo controlled, parallel group, multicentric, phase IIa clinical trial to evaluate the safety, tolerability and therapeutic efficacy of daily oral treatment with NFX88 on neuropathic pain in patients with spinal cord injury.
EudraCT nº	2018-004792-13
Study code	NFX88-2A-2018
Sponsor	NEUROFIX S.L.
Contract Research Organization	QualitecFarma®
Clinical phase	IIa (proof of concept)
Study Design	Multicentric, Randomized, Double Blind, Parallel Group (NFX88 vs Placebo-Controlled) Clinical Trial.
Study Type	Interventional
Anticipated start date	Q2 2019 (Jun2019)
Duration of Study	<p>Recruitment phase: ~6 months</p> <p>Completion of recruitment: Q3 2019 (Dec2019)</p> <p>End of the Study: Q2 2020 (Apr2020, 4 months after the last patient enrolled)</p>
Ethic Committee	Comité de Ética de Investigación con medicamentos Regional (CEIm-R) de la Comunidad de Madrid
Total number of Sites	<p>4 National sites have been pre-selected.</p> <p>Competitive recruitment.</p>
Study Population	Spinal cord injury patients with neuropathic pain.
Objectives	<p>Primary objective:</p> <p>The trial primary goal will be to evaluate the safety and tolerability of NFX88 in spinal cord injury patients with neuropathic pain over 90 days.</p> <p>Secondary objective:</p> <p>The trial will also explore the preliminary therapeutic efficacy associated with NFX88 through the analysis of validated</p>

measurement scales (VAS, PD-Q, PGIC).	
Planned number of patients and Study Arms	<p>Total: up to 60 completed patients</p> <p>A. Experimental Arms</p> <ol style="list-style-type: none"> 1) 1.05 g/day NFX88: 15 patients. 2) 2.10 g/day NFX88: 15 patients. 3) 4.20 g/day NFX88: 15 patients. <p>B. Control Arm</p> <ol style="list-style-type: none"> 1) Placebo: 15 patients.
Inclusion criteria	<p>Patients eligible for enrolment in the study must meet all the following inclusion criteria:</p> <ol style="list-style-type: none"> 1. Able and willing to provide written informed consent. 2. Male or Female 18 to 65 years of age. 3. Traumatic complete or incomplete spinal cord injury with C4-T12 level and more than three months since injury. 4. Diagnosed of neuropathic pain with an average pain score ≥ 4 measured using the VAS scale during the last week. 5. Stable treatment, for at least 1 month, with pregabalin 150-300 mg/day, that should be maintained at the same dose for 90 days until the end of the study treatment. 6. Normotensive patients defined as patients with blood pressure values between 90-160 for systolic pressure and 50-115 for diastolic pressure. 7. Patients who have been treated with stable doses of neuroactive drugs (antidepressants, anticonvulsants, antispastic and similar medicines) at least during the last month can also be recruited. 8. Availability for the entire study period, absence of intellectual problems likely to limit the validity of consent to participate in the study or the compliance with protocol requirements; willingness to adhere to the protocol requirements, ability to cooperate adequately, to understand and follow the instructions of the physician or designee. 9. Women who are not postmenopausal (at least 12 months) or surgically sterile must have a negative pregnancy test at screening and at the end of study and either abstain from sexual intercourse or use a highly effective method of birth control for the duration of the study and after 12 weeks after the last dose of study drug.

10. For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm for the duration of the study and after 12 weeks from the last dose of study drug.

Exclusion criteria	<p>Patients meeting any of the following criteria must <u>NOT</u> be enrolled in the study:</p> <ol style="list-style-type: none"> 1. Patients treated with opiates (major and minor) and cannabinoids (synthetic, natural or analogous). 2. Patients with blood pressure higher than those accepted in the inclusion criteria. 3. History of alcohol, drug abuse within 6 months prior to screening. 4. Psychiatric patients or those with moderate or severe cognitive impairment. 5. Patient who is pregnant or lactating. 6. Patient who shows evidence of significant liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects. 7. Patient who has clinically significant diseases and/or infections captured in the medical history or evidence of clinically significant findings on physical examination and/or clinically significant ordinary laboratory evaluations (haematology, biochemistry, and urinalysis) or ECG. 8. Patient who is currently participating in another clinical trial of an investigational drug or medical device within 90 days prior to screening. 9. Inability to comply with study protocol. 10. Patient unable to swallow tablets. 11. History of cancer except local basal or squamous cell carcinoma of the skin that has been excised.
Experimental drug	<p>NFX88</p> <p>Pharmaceutical Form: coated tablets</p> <p>Strength: 350 mg</p>
Control drug	<p>Placebo</p> <p>Pharmaceutical Form: coated tablets</p> <p>Strength: 0 mg</p>

Dosing regimen and treatment	<p>Doses:</p> <p>A. Experimental Arms</p> <ol style="list-style-type: none"> 1) 1.05 g/day NFX88 2) 2.10 g/day NFX88 3) 4.20 g/day NFX88 <p>B. Control Arm</p> <ol style="list-style-type: none"> 4) 0.00 g/day Placebo coated tablets <p>Frequency: 3 times a day (t.i.d.)</p> <p>Duration of the treatment: 90 days</p> <p>Total duration of the trial: 1-7 Screening days, 90 treatment days (approximately 3 months) and 30 Follow-up days</p>
Study assessments	<p>Assessment points:</p> <p>SV: Screening (-7days from V1), V1: randomisation (day 1 of treatment), V2: evaluation (30 +/- 3 days from V1), V3: evaluation (60 +/- 3 days from V1), EoT/WV: end of treatment (90 +/- 3 days from V1)/ withdrawal visit (any time), EoS/FU: end of study/follow-up (120 +/- 3 days from V1).</p> <p>Safety and tolerability:</p> <p>Safety and tolerability of NFX88 administered for 3 months will be assessed by the number, severity, and type of AE, including changes in:</p> <ul style="list-style-type: none"> - Vital signs (Time Frame: VS, V1, V2, V3, EoT or WV and FU/EoS). - ECG (Time Frame: SV, V2, V3, EoT or WV and FU/EoS). - Clinical laboratory parameters (Time Frame: SV, V2, V3, EoT or WV and FU/EoS). - Effect of NFX88 on spasticity score as determined by MAS (Time Frame: SV, V1, V2, V3, EoT or WV and FU/EoS). - Effect of NFX88 on sensory and motor function by ASIA scale (Time Frame: SV, V1, V2, V3, EoT or WV and FU/EoS). <p>Efficacy:</p> <p>Effect of NFX88 in changes of neuropathic pain reduction scales:</p> <ul style="list-style-type: none"> - VAS (Time Frame: SV, V1, V2, V3, EoT or WV and FU/EoS). - PD-Q (Time Frame: SV, V1, V2, V3, EoT or WV and

	FU/EoS).
	- PGIC (Time Frame: V3, EoT or WV)
Randomisation procedure	1: 1; 1: 1
Primary parameters	Safety and tolerability: the safety outcome measures for this study are: <ul style="list-style-type: none">- Incidence of serious adverse events- Incidence of severe adverse events- Incidence of specific laboratory abnormalities- Incidence of relevant changes in vital signs- Incidence of relevant changes in 12-lead ECGs- No changes in MAS and AIS scales.
Secondary parameters	Efficacy: The efficacy outcome measure for this section is: <ul style="list-style-type: none">- Improvement in neuropathic pain scales VAS, PD-Q, and PGIC.
Planned analysis	The planned analysis for the primary and secondary endpoints will be done when the last patient has completed treatment period.

1. BACKGROUND

Spinal cord injury (SCI) is a condition usually resulting from accidental causes affecting conduction of sensory and motor signals across the site(s) of lesion(s), as well as the autonomic nervous system. According to location and severity of damage along the spinal cord, the symptoms can vary widely, from pain or numbness to paralysis to incontinence. SCI worldwide incidence ranges from 3.6 to 195 cases per million inhabitants, depending on the geographic area of study. The prevalence of SCI in the European Union is around 2-3 cases per 10,000 inhabitants, showing also geographic differences (Singh et al., 2014). Based on neurological levels, different studies showed that ca. 30% patients are tetraplegic, ca. 55% are paraplegic and about 15% have Conus-Cauda Equina injury. According to the severity of the lesion, ca. 70% of SCI patients have complete lesions and about 30% have incomplete lesions (Afsar et al, 2014). Up to 70 % of patients with spinal cord injuries develop disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (spasticity) (Rekand T et al, 2012a) and over 80% patients reported the presence of pain: musculoskeletal pain (59%), at-level neuropathic pain (41%), below-level neuropathic (34%) and visceral pain (5%) (Siddall PJ et al, 2003). Although, neuropathic pain prevalence rates ranged from 26% to 96%, with a fairly even spread between these extremes (2009 Dijkers M et al, 2009; Rekand T et al, 2012b).

Neuropathic pain is defined as proposed by the International Association for the Study of Pain (IASP) as “pain initiated or caused by a primary lesion or dysfunction of the nervous system” (Merskey H & Bogduk N, 1994). In general, patients indicate that the worst life-quality worsening symptom is neuropathic pain (Hagen EM & Rekand T, 2015). It begins within the first few months of injury, and is usually progressive for about 3-5 years, before reaching a plateau and may persist for many years after the acute injury (Calmels P et al, 2009). The pain is usually severe in nature (VAS ≥ 7), and complicates treatments, impacts sleep, and mood. This neuropathic pain resulting in a substantial negative impact on patient function and quality of life (Baastrup C & Finnerup NB, 2008).

Post SCI pain may be very broadly attributable to increased neuronal excitability. This increased excitability may be due to either an enhancement of excitatory mechanisms or a loss or reduction in inhibition. A number of molecular changes will occur after SCI including changes in sodium ion channels, voltage-gated calcium channels, glutamate and gamma-aminobutyric acid (GABA) metabolism, serotonergic, noradrenergic, N-methyl-D-aspartate (NMDA) and opioid receptors. Drugs such as antiepileptics, tricyclic antidepressants and opioids have an effect on these changes. However, oral pharmaceutical intervention is often inadequate, commonly resulting in a reduction of only 20-30% in pain intensity (Baastrup C & Finnerup NB, 2008) and the side effects can be quite significant (Afsar et al, 2014; Teasell RW et all, 2010).

The most commonly recommended oral pharmacological agents for chronic pain fall into 3 major categories: antidepressants, anticonvulsants, and analgesics. Pregabalin (Lyrica®) is recommended as the first choice of first-line medications and Gabapentin (Fanatrex®, Gabapin®, Gabrion®, etc.) is recommended as the next choice when pregabalin is not an option or has been proven ineffective (Guy SD et al, 2016). However, in many instances other drugs are concomitantly prescribed in combination treatments that may have a negative impact on patient's hepatic health status. Treatment of topical agents such as capsaicin or lidocaine as

well as with intradermal Botulinum toxin injections may be useful approaches but need to be studied on populations with SCI. Further studies are needed for evaluation of efficacy of those measures on pain after SCI (Hagen EM & Rekand T, 2015).

Considering that (i) neuropathic pain affects more than 50% of individuals with SCI, (ii) being considered sometimes the major problem following SCI, (iii) that current pharmacological treatments are only partially successful in relieving pain, and (iv) taking in account that recent advantages in pain research indicate multiple mechanisms underlying the initiation and maintenance of neuropathic pain, it is possible to find a more rational treatment and potential new targets for therapeutic interventions in patients with neuropathic pain.

Synthetic lipid analogues were not considered of clinical interest until recently. However, (i) the protection of the CNS by the BBB (a succession of lipid membranes), (ii) the high amount of lipids in the CNS and (iii) the lipid nature of most inflammation mediators that worsen neurological damage, suggest the cell membrane is a promising target for pharmacological therapy and that rationally designed lipids could have application in the treatment of CNS conditions. NEUROFIX's design process is based in lipid-soluble and biocompatible molecules that can safely travel from the blood flow to the neurons and glial cells, reaching the CNS at nontoxic doses with no undesired effects. Specifically, our aim in this study is to explore the efficacy (Proof of Concept) of NFX88 in alleviate the neuropathic pain in spinal cord injury patients.

NFX88 is a small molecule, sodium- α -hydroxy-9-*cis*-octadecenoate (2-hydroxyoleic acid, 2OHOA, a non-hydrolysable oleic acid (OA) analogue), that regulates the production of lipid neuroinflammatory mediators through interaction with phospholipases and PPAR γ . Both entities are involved in regulation of enzymatic and GPCR-mediated signalling that prevents neuroinflammation, neuropathic pain in a rat model of spinal cord injury (Ávila-Martin et al., 2015). In addition, it participates in neuron growth factor expression induction and myelinization via its α -hydroxyl-carboxyl moiety, being more efficacious than pregabalin to reduce neuropathic pain in animal models (Ávila-Martin et al., 2015; Ávila-Martin et al., 2017).

1.1 Relevant preclinical results

1.1.1 2OHOA

The pre-clinical experience is fully described in the current version of the 2OHOA Investigator's Brochure.

Key findings are summarized below.

Analysis of the fatty acid composition from cell tumour lines (A549 human adenocarcinoma cells, S767 and U118 human glioma cells) shows that 2OHOA is preferentially incorporated into the glycerophospholipid fraction of the plasma membrane, particularly the phosphatidyl ethanolamine (PE) and phosphatidyl choline (PC) fractions, probably replacing its analogue oleic acid (Barceló-Coblijn et al, 2011; Martin et al., 2012). Based on the human liver microsomal enzymes in vitro studies on CYP450 inhibition, 2OHOA is believed to have a low potential to cause drug-drug interactions, though there is the potential for clinically important interactions with 2OHOA through its inhibition of CYP2C9. The results from the two CYP450 inhibition studies performed were inconclusive and therefore difficult to interpret.

For this reason, as a precaution certain concomitant medication was prohibited in the clinical trial already conducted in patients with cancer, protocol code MIN-001-1203 and, where concomitant use of other drugs metabolized by CYP2C9 was unavoidable, and subjects closely monitored as appropriate. However, due to its structure closely related to oleic acid, 2OHOA has been seen to be a very safe compound as doses up to 3 grams/kg per day (p.o.) did not cause deaths in rats (Terés et al., 2012). Recent data showed that, in addition to its incorporation to phospholipids, cholesterol esters or acyl-glycerols, 2OHOA is preferentially metabolized via α -oxidation, which yields as main metabolite heptadecenoic acid (17:1n-9), a fatty acid identical to oleic acid with 17 C atoms, instead of 18 (Fernandez-Garcia et al., 2018).

The dog disposition of 2OHOA was observed at the three tested doses (100, 400 and 1,000 mg/kg/day) on days 1 and 28 of treatment. Quantifiable levels were seen at 0 h on day 28 and 2OHOA was still present in plasma at 144 hours after the last dosing. The systemic exposure to 2OHOA was influenced by the administered dose level and by the duration of treatment. The mean accumulation ratios calculated for 400 and 1,000 mg/kg/day dose groups indicated a slight trend towards drug accumulation, especially at the dose of 400 mg/kg/day due to a high individual variability. 2OHOA did not show a trend toward accumulation in the 100 mg/kg /day dose group for which an overall accumulation ratio of 1.16 was calculated. A slight influence of the sex on the extent of exposure was observed after the administration of 2OHOA. In general, females showed a higher systemic exposure to the drug at the dose levels of 100 and 1,000 mg/kg/day but no clear influence of sex was observed at the intermediary dose of 400 mg/kg/day. Calculated elimination half-lives at low and intermediate doses were similar, both for day 1 and day 28. Values ranged between 7.10-11.21 hours for low dose and 6.76-8.68 hours for intermediate dose. Elimination half-life could not be calculated on day 1 at the highest dose but was 66.16 hours on day 28 at the dose of 1,000 mg/kg. This last half-life value was calculated from the recovery animals 15M, 16M, 31F and 32F in which blood collection was done up to 144 hours after last dosing on day 28. The mean residence time correlated with the findings observed for the elimination half-life. The rat disposition of 2OHOA was observed at the three tested doses (40, 245 and 1500 mg/kg/day) on days 1 and 28 of treatment. Systemic exposure was influenced by the administered dose level and by the duration of treatment. No influence of the sex on the extent of exposure was observed after the administration of 2OHOA. The half-life values suggested that the administered dose influenced the elimination half-life of 2OHOA, with the elimination half-life being longer as the dose increased from 40 to 1500 mg/kg, suggesting a saturation of the clearance processes. However, the half-lives obtained on days 1 and 28 for the dose of 245 mg/kg were similar (3.47 and 3.67 hours), suggesting that the duration of treatment did not influence the elimination of 2OHOA. The mean residence time was higher as the dose increased from 40 to 1,500 mg/kg.

The blood distribution of 2OHOA (cell pellet, free in plasma and bound to plasma proteins) was determined in blood obtained from Wistar rats. The results show that [³H]2OHOA was mainly bound to plasma proteins (75.2% when trichloroacetic acid (TCA) was used for precipitation and 63.8% when it was used Methanol), it was also incorporated to blood cells (21.6% with TCA and 27.8% with methanol) and a small part was free (1.4% with TCA and 8.8% with methanol) in plasma.

The tissue distribution was determined in NUDE (Swiss) Crl:NU(Ico)-Foxn1nu mice which developed SF767 cells-derived tumors after oral dosing of [³H] 2OHOA. The doses used for oral administration by gavage were 100, 200 and 600 mg/kg administered every 24 hours during 1, 7 and 28 days of treatment. Organ samples were obtained at the end of the treatments (1, 7 and 28 days). The results show a dose- and time-dependent accumulation of [³H]2OHOA in all organs studied including brain and tumours. The accumulation of radioactive product/metabolite was determined in feces of nude mice treated for 28 days with 100, 200 and 600 mg/kg/day. From this data it can be concluded that 2OHOA and/or its metabolites is/are excreted in faeces, and that there is a dose-dependent relationship in the amount of product measured in faeces.

1.1.2 Experimental animal models of SCI

Sensorimotor dysfunction following incomplete SCI is often characterized by paralysis, spasticity and pain (Gómez-Soriano J et al, 2016). Intrathecal (i.t.) administration of the albumin-oleic acid (A-OA) complex in rats with SCI, produced partial improvement of these symptoms (Ávila-Martin G et al 2011). Comparison of the expression between healthy, SCI, and SCI rats treated with A-2OHOA (albumin-2-hydroxyoleic acid) revealed relevant changes in the expression of genes associated with neuronal morphogenesis and growth, neuronal survival, pain and inflammation (Ávila-Martin et al., 2017).

NFX88 (2OHOA) it has been seen that reduces neuropathic pain, both after p.o. or i.t. treatments (Ávila-Martin et al., 2015; Ávila-Martin et al., 2017). The efficacious in the modulation of nociception and prevent a pain-related anxiety in the spared nerve injury (SNI) model in Wistar rats, is mediated by an inhibition of spinal dorsal horn microglia activation (Ávila-Martín G. et al. 2015).

The analgesic effect of 2OHOA on both nociceptive and cerebrally mediated behavioural tests was assessed at a dose of 400 mg/kg. This dose was chosen according to previous studies, which demonstrated that 2OHOA was antihypertensive when administered in rats between doses of 100-900 mg/kg, p.o., every 12 h for 7 days (Alemany et al, 2006), and a lack of obvious toxic effects based on cytohistological analysis of different organs following administration at 600 mg/kg in Sprague Dawley rats (Alemany et al, 2004) and at 1,200 mg/kg, p.o. every 12 h for 7 days in athymic nude mice (Martinez et al., 2005).

1.1.3 Summary of toxicological data

2OHOA has been tested in a standard range of safety pharmacology studies ie, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Respiratory System

There was no effect of 2OHOA on **Respiration Rate** and **Tidal Volume** in male **Wistar rats** following a single dose with 40 and 245 mg/kg of oral 2 OHOA. At a dose of 1,500 mg/kg, 2OHOA had effects on respiratory function of freely moving conscious rats. The effects included a decrease in respiratory rate, an increase in tidal and minute volumes and the appearance of clinical signs. Clinical signs included the pushing of their noses along the

bottom of the chamber, shaking their heads, longer pauses between breaths and gasping for breath.

Cardiovascular System

The 14-Day oral (capsules), toxicokinetic and safety pharmacology study in Beagle dogs comprised 6 groups with 2 males and females each: (1) 0 mg/kg/day, (2) 20 mg/kg/day, (3) 200 mg/kg/day, (4) 600 mg/kg/day, (5) 900 mg/kg/day and (6) 1,200 mg/kg/day. There were 3 cases where QT and QTc prolongation comparing day 1 and day 13 measurements could be observed (1 female dosed at 600 mg/kg/day and 1 female and 1 male dosed at 1,200 mg/kg/d). No similar cases were seen in groups 1, 2, 3 or 5. No clear pattern of dose-dependent effect on cardiac repolarization was identified.

The 28 Day oral (capsules) toxicity study in Beagle dog study comprised 4 groups: groups 1 and 4 (with 5 males and 5 females, each) and groups 2 and 3 (with 3 males and 3 females, each). The following doses were administered: (1) 0 mg/kg/day, (2), 100 mg/kg/day, (3) 400 mg/kg/day and (4) 1,000 mg/kg/day. Administration of 2OHOA for a period of 4 weeks at the dose of 1,000 mg/kg/day led to changes in the electrocardiogram: a left bundle branch block-like pattern was seen in all five males in this group, and three of 5 females before and after dosing in week 4 of treatment. Macroscopic changes in the heart were seen in two males in this dose group, and in one female in the 400 mg/kg/day group. Furthermore, chronic myocarditis was observed in two males and two females after 4 weeks of treatment with 2OHOA (1,000 mg/kg/day). There were no histopathological findings in other dose groups. Similar changes were not present in animals undergoing a 3-week recovery period and therefore these changes are considered reversible.

The effect of 2OHOA on hERG tail current recorded from stably transfected HEK293 cells study incubations of 2OHOA were made at concentrations of 1, 3, 10 and 30 μ M. The conclusion of the study that 2OHOA produced slight inhibition of hERG channels at 0.24 μ M (corresponding to nominal concentration of 1 μ M) is possibly misleading. Other in vitro studies show similar effects of fatty acids on hERG channels (Guizy et al, 2005; Den Ruijter et al, 2010). Notwithstanding that, it is well known that fatty acids are not arrhythmogenic, and their net effect, based on molecular, physiological and clinical data, has been shown to be cardio protective as a consequence of their beneficial effects on the lipid profile. Importantly, the isolated cases of QT prolongation from in vivo studies in dogs were observed only at very high doses (at least 600 mg/kg/day p.o), much larger than the exposure to subjects in the proposed study. Collectively, this information does not seem to indicate a **cardio-toxic effect** of 2OHOA.

The effects of 2OHOA on behavioural and physiological response were assessed by the modified Irwin study at doses of 100, 300 and 1,000 mg/kg following oral administration in the mouse. No effect was observed in any control animals or in any of the animals treated with 2OHOA at these doses. Mortality was not observed in any of the treatment groups.

1.1.4 Acute Toxicity

In acute single dose toxicity studies to determine the minimum lethal dose (MLD) and maximum non-lethal dose (MNLD), 2OHOA was administered orally at a dose of 3,000 mg/kg in Wistar rats and CD-1 mice. No mortality was recorded in these studies. As it was considered that 3,000 mg/kg was a sufficiently high dose, the MNLD and MLD were not

determined, but it was concluded that the MLD is considered to be greater than 3,000 mg/kg in these species. Following acute i.p. administration in rats at doses up to 700 mg/kg, the MNLD was established to be 125 mg/kg and the MLD at 250 mg/kg.

1.1.5 Repeat-Dose Toxicity Studies

Rat: Oral administration of 2OHOA for 28 days at the of 40, 250 and 1,500 mg/kg/day to rats at dose levels up to 1,500 mg/kg caused salivation which was attributed to the taste of the investigational substance. At the highest dose, treatment-related clinical signs were observed, and haematological and biochemical changes were recorded (increased levels of bilirubin and various enzymes) as well as histopathology of several organs. In rats treated with 245 mg/kg slight blood biochemical changes were observed. In the 40 mg/kg dose group a lower sperm count was observed at the end of treatment which had recovered at the end of the recovery period. Based on this, 40 mg/kg/day 2OHOA can be established as the NOAEL in rats.

Dog: Oral administration of 2OHOA for 28 days at 100, 400 and 1,000 mg/kg/day to dogs produced no findings related to the cardiovascular system except at the highest dose of 1000 mg/kg/day. There were also dose-dependent effects on the GI tract consisting mainly of loose faeces and discoloured diarrhoea and vomiting. 2OHOA administration led to an increase in aspartate transaminase (AST) / alanine transaminase (ALT) / CK parameters in males and females treated with 600 mg/kg/day. No treatment-related effects were recorded in haematology, coagulation and urine parameters or on organ weights. In view of these results, taking into account the cardiac effects present in electrocardiographic and histopathological evaluations, as well as the changes in biochemistry parameters and the clinical signs noted, the NOAEL in dogs can be defined as 400 mg/kg/day.

A standard battery of genetic toxicology studies has established that 2OHOA is not genotoxic.

Carcinogenicity, reproductive and developmental toxicity studies will be completed at later stages of development.

1.2 Overview of Clinical Studies

The API contained in NFX88 is the same as the molecule present in LP561 (i.e., 2-hydroxyoleic acid), which successfully completed a phase I study in humans with advanced solid tumours. This is an investigational medicinal product (IMP) currently authorized in Spain for the use in humans in the context of clinical trials. Both NFX88 and LP561 have oral administration, being the dose used with LP561 in clinical trials (up to 16 g per day, p.o., b.i.d.) much higher than those to be used in the present study (up to 4.2 g per day, p.o., t.i.d.).

The phase I clinical trial to investigate the safety, tolerability and exploratory therapeutic efficacy of 2OHOA in adult patients with advanced solid tumours was the first study in patients and has now been completed. 2OHOA was administered to 54 patients (32 patients in the Dose Escalation Phase to determine the maximum tolerated dose (MTD) of 2OHOA and 22 patients in the Safety Expansion Phase of the study to identify the Recommended Phase II dose (RP2D) of 2OHOA. Five sites participated in the study, three in Spain and two in the UK.

Data from seven dose cohorts (0.5, 1, 2, 4, 8, 12, and 16 g of 2OHOA daily) indicates that the study drug is generally well-tolerated apart from some anticipated gastrointestinal (GI) effects (mainly low-grade diarrhoea, nausea and vomiting; grade 1 or 2) in the high dose cohorts. In

one subject (Grade 3 diarrhoea) from cohort #6 (12 g/day), and in 3 patients (Grade 2 or 3 GI AEs) from cohort #7 (16 g/day) which were either probably or certainly related to the study medication. The DLTs observed in these four patients, meant that the MTD had been reached. The MTD was defined as 12 g/day of 2-OHOA.

There were no serious adverse reactions (SARs) reported. A total of twenty-one serious adverse events (SAEs) were recorded, none of which was considered to be related to the study drug. There were no safety findings which were a cause of concern.

Pharmacokinetic data after single and repeat b.i.d. and t.i.d oral administration in fasted state, the 2OHOA absorption was rapid showing a median T_{max} value of 1 hour, which was delayed in fed state (2-6 hours). The single dose administration of 2OHOA in fed state reduced the mean C_{max} around 18-34% but did not show a significant effect on the AUC.

Following single and repeat dosing of 2OHOA, there was dose proportionality in terms of C_{max} and AUC within the dose interval evaluated (0.5-16 g as total daily dose). After oral dosing, the volume of distribution at steady state (V_{ss}/F) and the plasma clearance (Cl/F) were around 105 L and 26 L/h, respectively. The accumulation ratio based on AUC (RAUC) was around 1.5 and 2 after repeat b.i.d. and t.i.d administration, respectively. Based on this accumulation ratio, the effective half-life of 2OHOA was calculated to be around 8-9 hours.

In summary, from a safety perspective, there has been exposure of a significant number of patients over a substantial period to the study drug and 2OHOA showed a favourable safety profile to date with dose limiting toxicity (DLT) emerging at the highest doses selected. The adverse event pattern and death rate due to progressive disease (PD) were as expected in this type of terminal cancer patient population. On the basis of the data reviewed in the latest DSUR and up to conclusion of the study, there are no findings that change the benefit/risk profile of 2OHOA. The safety profile of the 2OHOA remains acceptable for the intended clinical indications.

1.3 Evaluation of the patient with spinal cord injury

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), published by the American Spinal Injury Association (ASIA), is widely used to document sensory and motor impairments following SCI (Kirshblum et al, 2011). The International Standards examination used for neurological classification has two components (sensory and motor), which are separately described below. These elements are used in determining the level and degree or severity of the SCI.

Generally, the higher up the level of the injury to the spinal cord, the more severe the symptoms. Tetraplegia refers to impairment or loss of motor and/or sensory function in the cervical segments of the spinal cord due to damage of neural elements within the spinal canal. Tetraplegia results in impairment of function in the arms as well as typically in the trunk, legs and pelvic organs, i.e. including the four extremities. Paraplegia refers to impairment or loss of motor and/or sensory function in the thoracic, lumbar or sacral (but not cervical) segments of the spinal cord, secondary to damage of neural elements within the spinal canal. With paraplegia, arm functioning is spared, but, depending on the level of injury, the trunk, legs and pelvic organs may be involved. The term incomplete injury is used when the degree of impairment results in the preservation of any sensory and/or motor function below the

neurological level that includes the lowest sacral segments S4-S5. Complete injury is used when there is an absence of sensory and motor function in the lowest sacral segments (S4-S5).

The traumatic injury occurred in the cervical spine in 54% of the cases, in the thoracic spine in 25%, and in the lumbar spine in 22%. The degree of impairment according to AIS was degree A (Complete injury) in 26% of the cases, degree B (Sensory incomplete) in 26%, degree C (Motor incomplete) in 19%, D (Motor incomplete) in 27% and E (Normal.) in 2% (Null A et al, 2017). One of the first signs of neurologic deterioration is the extension of the sensory and motor deficit cephalad. Moreover, spasticity may appear or worsen along time after injury. The most commonly used tools to evaluate the severity of injury and spasticity in clinical trials among patients with SCI are the ASIA and Modified Ashworth Scale (MAS), respectively (Craven BC and Morris AR, 2010). The AIS scale was developed by the ASIA in 2006 as part of the ASIA- ISNCSCI (Kirshblum et al, 2011). The MAS originally developed by Ashworth B et al, (1964) and subsequently modified by Bohannon and Smith (1987), is a six-category ordinal scale used to assess the resistance encountered during passive muscle stretching that does not require instrumentation and is quick to perform.

Pain assessment in individuals with SCI is complex and requires a combination of standard general pain assessments, as well as medically specific questions unique to the patient's pathophysiology (Lee S et al, 2013). The most commonly used tools to evaluate the efficacy of pharmacologic interventions for treatment of pain among patients with SCI, includes: Visual Analogue Scale (VAS), Patient Global Impression Change (PGIC) and PainDETECT questionnaire (PD-Q).

VAS scale has been shown to be reliable and valid in the assessment of pain severity and is well accepted by pain researchers and clinicians (Teasell RW et al, 2010). The 7- point Guy/Farrar PGIC (Guy W, 1976; Farrar JT et al, 2001) is recommended as the outcome measure of the global improvement of pain (Bryce TN et al, 2017). The PD-Q consists of 7 questions that address the quality of neuropathic pain symptoms (Mathieson S and Lin C, 2013), was primarily validated in German (Freynhagen R et al, 2006) and subsequently validated in several languages, including Spanish (De Andrés J et al, 2012). PD-Q was recommended as complementary neuropathic pain assessment tool in SCI to monitor pain severity and/or its time-dependent course, providing evidence that the scope for PD-Q can be expanded to individuals with SCI (Franz S et al, 2017).

2. STUDY RATIONALE

Usually, patients report neuropathic pain either after the medullary lesion or a few months later. The usual patient managing is receiving treatment with an increasing number of drugs, such as pregabalin, amitriptyline, gabapentin, and others (Hagen & Rekand, 2015; Singh et al., 2014). These compounds cause relevant side effects, such as nausea, somnolence, dry mouth and/or eyes, constipation, cardiotoxicity, sedation, gastro-intestinal effects, dizziness, rash, headaches, peripheral oedema, etc. None of these side effects have been reported for NFX88 at therapeutic doses in the previous phase I clinical trial for other indication, and if the phase II study proposed demonstrates the same efficacy observed in animals, an improvement in the quality of life would be expected for those patients when managing neuropathic pain with this compound. In fact, NFX88 was found to be more efficacious than pregabalin in an animal model of neuropathic pain (Ávila-Martin et al., 2015). Therefore, due its high safety and tolerability profile in human and its potential higher efficacy with respect to reference drugs, it

is reasonable to investigate the potential efficacy and the safety and tolerability for the treatment of neuropathic pain in patients with SCI.

2.1 Risk / Benefit Assessment

The studies carried out with NFX88 demonstrate its efficacy in animal models and its safety in humans. This clinical trial will provide proof of concept about the safety, tolerability and efficacy in humans, specifically, it will shed light on the efficacy of NFX88 for the treatment of neuropathic pain in patients with spinal cord injury. At this moment, neuropathic pain management is carried out with drugs initially purposed for other conditions. Due to low prevalence, spinal cord injury is considered an orphan disease for which the number of treatments available for the different symptoms it causes is limited.

The working hypothesis is that the treatment with NFX88 will be safe and well tolerated in patients with spinal cord injury, as demonstrated in the phase I / II study previously conducted in patients with cancer. For that reason, we will evaluate the tolerability, safety and effectiveness of NFX88 in the relief of neuropathic pain in patients with spinal cord injury. It is expected that the NFX88 will be superior to placebo (both plus pregabalin as common treatment) which would avoid the addition of different drugs in the management of this type of patient with the consequent reduction of the well-known side effects. Therefore, it is expected that the treatment with NFX88 will demonstrate a reduction in neuropathic pain determined by validated questionnaires.

2.2 Dose Justification

This molecule has been previously tested in humans up to doses of 16 g per day (p.o.) and has demonstrated high safety. Moreover, in a pilot study with 5 subjects, 3 reported benefit against pain in a range of 0.5-2 g per day (unpublished results).

In an animal model of neuropathic pain, it was observed the maximum NFX88 efficacy at a daily dose of 400 mg/kg (p.o.). According to the FDA dose equivalence tables (2005), this dose would correspond in humans to about 60 mg/kg, which would be about 4 g per day (p.o.). In the present study, it is planned to investigate from 1.05 up to 4.20 g per day (p.o.), doses that proved to be safe in the phase I study carried out in humans with advanced solid tumors.

The previous data from phase I study indicates that the study drug is safe and generally well tolerated at doses range to proposed will be used in this phase 2A clinical trial. The GI effects in the phase I study were observed at the high dose cohorts (12 and 16 g/day). In that case, the GI symptoms could had been the result of the high amount of excipients in the formulation, such as mannitol (ca. 15 g per day at dose of 16 g/day of 2OHOA). However, in this clinical trial, the doses range to be used will much lower than that dose (1.05-4.20 g/day). Taking in account that the amounts of API and excipients will be below that previously used, the company does not anticipate any relevant adverse events and considers no additional studies for NFX88 will be needed. Although we do not expect adverse effects, if any adverse effect related to gastrointestinal tract or of any other nature appear, it will be handled based on the physician's criteria with standard medication. Before the first patient enrolled, a steering committee (SC) will be constituted to evaluate safety and tolerability data of patients in the trial. Any serious adverse event will be assessing, and the SC could decide patient treatment discontinuation or any other urgent measure.

3. STUDY OBJECTIVES

This proof-of-concept clinical trial is carefully designed to establish the safety profile of NFX88 in neuropathic pain after spinal cord injury (SCI) and explore the relationship between three (1.05, 2.10 and 4.20 g) doses administered and the induction of improvement in neuropathic pain, based on the score obtained using the specific questionnaires to evaluate pain.

In summary, this small-scale study is designed to demonstrate that the NFX88 is safe and well tolerated, as well as preliminary evidence of improvement in the score of VAS, PD-Q, and PGIC scales.

3.1 Primary Objective

The primary objective is to assess the safety and tolerability of NFX88 in spinal cord injury patients with neuropathic pain over ninety-day treatment period.

3.2 Secondary Objective

The secondary objective is to explore the preliminary therapeutic efficacy associated with NFX88 through the analysis of validated measurement scales: VAS, PD-Q and PGIC.

4. STUDY DESIGN

4.1 Study Overview

This is a Phase IIa (proof of concept), randomized, double-blind, placebo controlled, parallel group, multicentric, clinical trial to evaluate the safety, tolerability and efficacy of daily oral treatment with NFX88 in SCI patients who are not receiving opiates or cannabinoids and present neuropathic pain with an average pain score ≥ 4 measured with a VAS scale during the last week at screening

Up to 60 completed patients are planned. Each subject will be administered with four tablets of study drug three times a day through 90 days. Enrolled patients, whom will continue their pre-established dose of pregabalin (range between 150 up to 300 mg/day), will be randomized to receive one of the doses of NFX88 or placebo. Subjects will be assigned to the treatments in random order. Evaluations will be taken at screening and at each of the 5 study evaluation visits.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

- Experimental treatment NFX88 at the following doses 1.05, 2.10 and 4.20 g/day
- Placebo

A schematic diagram of the study design is shown in Figure 1. The Schedule of Study Visits is presented in Table 1. See protocol sections 7 and 8 for full details of assessments and procedures. Visit windows ± 3 days will be allowed in this protocol for all the visits scheduled.

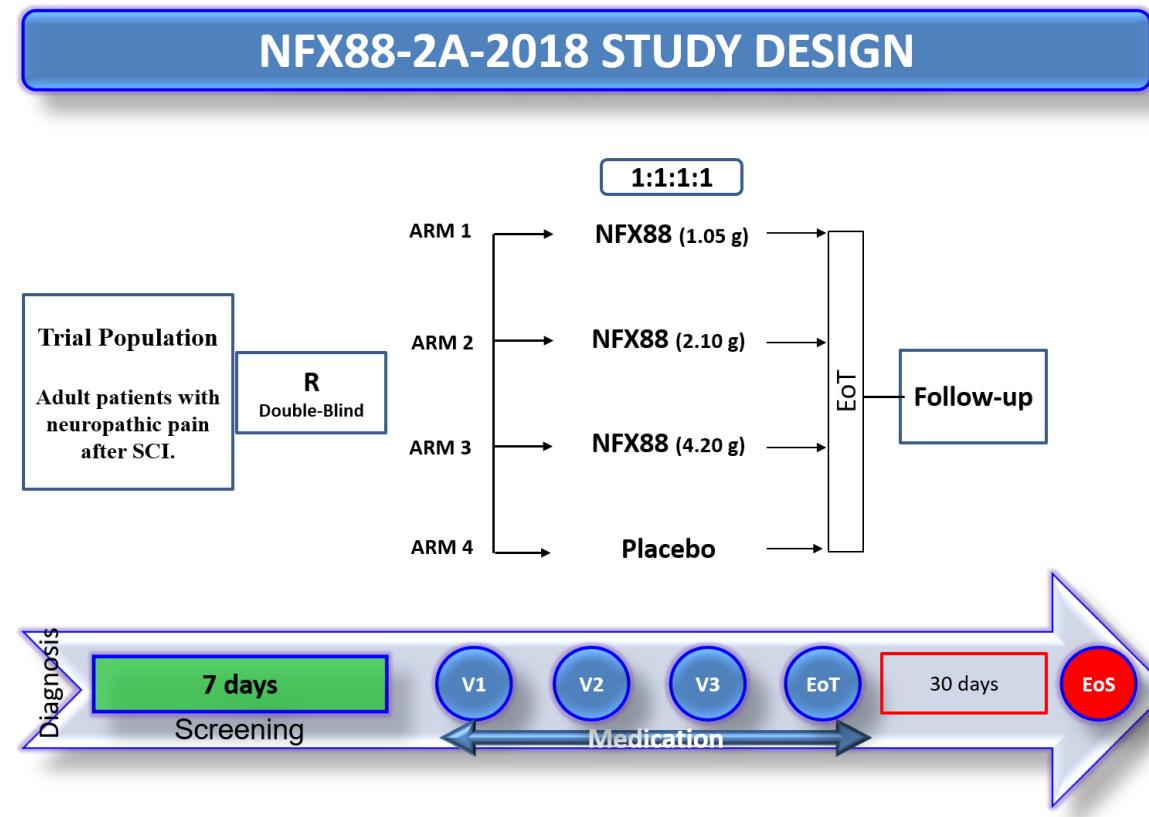


Figure 1. Schematic Diagram of the Study Design

If the patient misses an administration or visit for any reason, it should be documented as missed on the electronic Case Report Form (eCRF) and the visit rescheduled as soon as possible and/or continued with the next dose of the medication.

The patient can be considered evaluable when he/she adheres to the protocol in at least 75% of the treatment with NFX88 or placebo (at least 68 days of complete doses treatment) and not forgotten more than one week of consecutive doses. It is very important to avoid those forgotten doses. Patients who become “not evaluable” for this reason will be considered as “drop outs” in the protocol analysis and will be substituted by a new patient allocated to the same treatment arm. However, data from drop out patients should be included for intention to treat analysis.

4.2 Visit sequence:

Patients will be examined in 6 scheduled visits (see section 8 for specific measurements taken in each visit):

1. SV: Screening visit at day -7 of randomisation
2. V1: Randomisation visit this is day 1 of treatment
3. V2: Evaluation visit on day 30 +/- 3 after V1
4. V3: Evaluation visit on day 60 +/- 3 after V1
5. EOT: End of treatment visit on day 90 +/- 3 after V1

6. FU: Follow-up visit after end of treatment on day 120 +/- 3 after V1
7. WV: Withdrawal visit only for those who withdraw before EOT visit.

4.3 Screening/Baseline

Patients should undergo a baseline visit within 7 days prior to their study randomisation. The Principal Investigator or his/her designee will obtain written informed consent before any study related procedures are performed.

4.4 Randomisation

Eligible patients will be randomized into the study on visit 1 (V1), to start with the study medication the same day (V1), following the procedures described in section 6.3 (Method of Assigning Subjects to Treatment Groups) of this protocol.

4.5 Treatment Period

The administration of the oral treatment will be carried out daily under the patient's responsibility. The accountability of study drug will be recorded in the medical record during study visits at Site. Patients will begin the study treatment on V1 and will take four tablets three times a day of the investigational drug or placebo. The last visit of the treatment will be made 90 days after the first treatment date (visit window \pm 3 days). See protocol section 7.4. (Drug Administration Procedure) for more drug administration details.

During the treatment period the patient shall attend four visits to the Site: during V1, V2, V3 and EOT (window of \pm 3 days are permitted) and to carry out the assessments and procedures noted on Table 1.

However, patients will be advised to return to the clinical site for an unscheduled visit, if judged necessary by the physician in charge, for safety reasons.

Changes in VAS and PD-Q score induced by NFX88 treatment compared to placebo will be clinically evaluated by SV, V1, V2, V3, EoT or WV and FU/EoS. PGIC score will be evaluated by V3 and EoT or WV. See section 7.6 (Efficacy Measurements) for details of scales.

Reasonable effort should be made to comply with protocol assessments and procedures the designated days in order to avoid patient will attend visits at site more frequently than in a monthly basis.

A beta HCG serum pregnancy test will be performed at screening date to have the test results prior to drug administration. The pregnancy test will be repeated at the end of the study or during the withdrawal visit (find more details in protocol section 7.2.4 (Pregnancy Test).). A urine pregnancy test will be made the date of randomisation to women who are of childbearing age.

4.6 Follow-Up / End of Study

After completion of the Treatment Period, all patients will be followed up to assess evaluation of disease, if applicable, drug-related events, and patient evaluation according to Good

Clinical Practices and WHO guidelines. Patients will attend the study site to perform a follow-up visit, 120 days (\pm 3 days) after V1, randomisation day.

For patients whose participation in this clinical study is discontinued during the course of the trial, every effort will be made to perform the post-study tests as soon as possible after discontinuation.

The physician in charge will assess each routine laboratory test. In case of an abnormal value, the clinician will determine if it is clinically significant or not. Clinically significant laboratory values will be reported as adverse events on the eCRF. The laboratory values will be included in the clinical final report.

4.7 Study Outcome

4.7.1 Safety Endpoints

Safety and tolerability of NFX88 administered for 90 days will be evaluated by assessing the number, severity, and type of AE, including changes in vital signs, safety laboratory values, ECGs, and MAS (e.g. to monitor spasticity worsening) and ASIA (e.g. to monitor neurological worsening) scores.

4.7.2 Efficacy Endpoints

Efficacy of NFX88 treatment compared to placebo in pain improvement will be measured as:

- Reduction from V1 to EoT in pain intensity in the VAS scale.
- Reduction from SV to EoT in the likelihood of neuropathic pain in PD-Q scale.
- Global improvement at EoT in patient's condition according to the PGIC scale.

5. SELECTION OF STUDY POPULATION

5.1 Study Population

Male or Female 18 to 65 years of age, with spinal cord injury due to complete or incomplete C4-T12 trauma for more than three months. Diagnosed of neuropathic pain with a pain score \geq 4 in VAS scale during the last week prior to randomisation date, and who have stable treatment, for at least the last month with pregabalin in the range of 150 up to 300 mg/day.

Patient who withdraws subsequent to the screening assessments but before receiving the investigational product will not be considered in the statistical analyses, but they will be included in the eCRF as Screening Failure (SF). Patients that drop out after randomisation will be substituted as explained in section 5.7 (Replacement of Subjects) of this protocol.

5.2 Sample Size and Power

Patients will be included in the study up to achieve sixty (60) completed patients (1:1:1:1, treatment arm: placebo arm ratio) as described in section 6.3 (Method of Assigning Subjects to Treatment Groups) of this protocol. The main objective of the trial is to detect adverse events (AE) in the group with medication (45 patients) compared with placebo (15 patients). The power of this trial is the probability to see cases of AE caused by the drug in the treatment arms. This power depends on the true (unobservable) risks of those AE (the higher the risk the higher the chances of seeing cases). The table below shows the power of the trial to show

cases of AE depending of the true unobservable risk. For example, if the true risk of a certain adverse event while on treatment was 5% then we would have a probability of 68% of finding at least one of these events in the intervention arm, but if the true risk was 5% then we would have a 90% chance of finding this event in the trial. For higher true risks the power is even higher.

True unobservable Risk of AE of patient in treatment arm	2.5%	5%	10%	15%
Prob. of seeing at least one case of the AE (power)	68%	90%	99%	99.9%

5.3 Inclusion Criteria

Patients eligible for enrolment in the study must meet all the following inclusion criteria:

1. Able and willing to provide written informed consent.
2. Male or Female 18 to 65 years of age.
3. Traumatic complete or incomplete spinal cord injury with C4-T12 level and more than three months since injury.
4. Diagnosed of neuropathic pain with an average pain score ≥ 4 measured using the VAS scale during the last week.
5. Stable treatment, for at least 1 month, with pregabalin 150-300 mg/day, that should be maintained at the same dose for 90 days until the end of the study treatment.
6. Normotensive patients defined as patients with blood pressure values between 90-160 for systolic pressure and 50-100 for diastolic pressure.
7. Patients who have been treated with stable doses of neuroactive drugs (antidepressants, anticonvulsants, antispastic and similar medicines) at least during the last month, can also be recruited.
8. Availability for the entire study period, absence of intellectual problems likely to limit the validity of consent to participate in the study or the compliance with protocol requirements; willingness to adhere to the protocol requirements, ability to cooperate adequately, to understand and follow the instructions of the physician or designee.
9. Women who are not postmenopausal (at least 12 months) or surgically sterile must have a negative pregnancy test at screening and at the end of study and either abstain from sexual intercourse or use a highly effective method of birth control for the duration of the study and after 12 weeks after the last dose of study drug.
10. For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm for the duration of the study and after 12 weeks from the last dose of study drug.

5.4 Exclusion Criteria

Patients meeting any of the following criteria must NOT be enrolled in the study:

1. Patients treated with opiates (major and minor) and cannabinoids (synthetic, natural or analogous).

2. Patients with blood pressure higher than those accepted in the inclusion criteria.
3. History of alcohol, drug abuse within 6 months prior to screening.
4. Psychiatric patients or those with moderate or severe cognitive impairment.
5. Patient who is pregnant or lactating.
6. Patient who shows evidence of significant liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects.
7. Patient who has clinically significant diseases and/or infections captured in the medical history or evidence of clinically significant findings on physical examination and/or clinically significant ordinary laboratory evaluations (haematology, biochemistry, and urinalysis) or ECG.
8. Patient who is currently participating in another clinical trial of an investigational drug or medical device within 90 days prior to screening.
9. Inability to comply with study protocol.
10. Patient unable to swallow 12 1-gram tablets.
11. History of cancer except local basal or squamous cell carcinoma of the skin that has been excised.

5.5 Withdrawal Criteria

The patient will be advised in the Informed Consent Form (ICF) that they have the right to discontinue treatment or withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's, or the Sponsor's discretion at any time in order to protect their health.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Patients who are withdrawn from the study may be replaced, please refer to study statistical plan for more details.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data and study medication.

In the event that the patient drops out of the study or is withdrawn from the study, the withdrawal date and reason should be properly documented by the Investigator or his/her designee in the medical chart and eCRF.

5.6 Criteria for Removal of a Subject

Participation in the clinical study and/or treatment could be discontinued by the physician in charge of the study or by the sponsor for any of the following reasons:

- Serious adverse event.
- Significant protocol deviation (e.g. dosing regimen compliance, failure to comply with clinic visits scheduled).

- Routine laboratory value (s) greater than or equal to 4 times the reference values or if it is clinically significant.
- Pregnancy.
- The subject is uncooperative during the study.
- The patient's death

Details of reasons for removal patients will be recorded in the eCRF, reported to the Sponsor and documented in the medical chart and clinical study report.

5.7 Replacement of Subjects

Whenever a patient dropped out of the study, after randomisation but before end of treatment, for any of the reasons mentioned in this protocol, a new patient who meets criteria will be allowed to be enrolled to replace the lost participant whenever possible to complete the study sample size ensuring at least 15 patients for each arm with complete follow up. The new patient will be assigned to the same arm as the patient that has dropped out. The data from the drop-out patient will be kept and analysed. Please refer to study statistical plan for more details.

6. STUDY TREATMENTS

6.1 Identity of Experimental Drug

The drug substance is the sodium salt of 2-hydroxy-9-cis-octadecenoic acid (2OHOA)

6.1.1 Chemical Name

2-hydroxy-9-cis-octadecenoic acid sodium salt

6.1.2 Chemical Structure

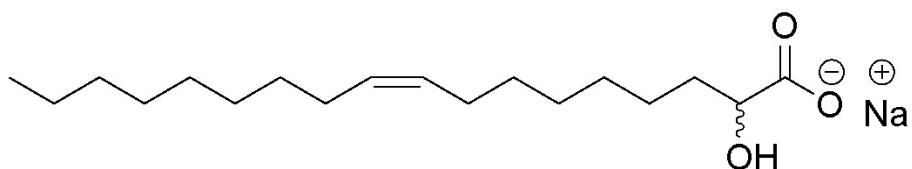


Figure 2. Chemical structure of 2OHOA.

6.1.3 Molecular Formula and Molecular Weight

C₁₉H₃₃O₃Na; MW 320.44

6.1.4 Arms of Treatment and Regimens

Total: up to 60 completed patients

A. Experimental Arms

- 1) 1.05 g/day NFX88: At least 15 patients.
- 2) 2.10 g/day NFX88: At least 15 patients.
- 3) 4.20 g/day NFX88: At least 15 patients.

B. Control Arm

4) Placebo: At least 15 patients.

6.1.5 Qualitative and Quantitative Composition

Name: NFX88

Active ingredient: 2OHOA (2-Hydroxy-9-cis-Octadecenoic Acid or 2-Hydroxy Oleic Acid)

Evaluating doses: 1.05, 2.10 and 4.20 g/day

Pharmaceutical form: 350 mg coated tablet

Posology: three times a day (at meal times: breakfast, lunch and dinner)

Presentation: Triflex (PP/AL/PVC/PVDC)/Aluminium unit dose blisters containing 12 x 1 tablet

Excipients dose: 890 mg

Manufactured by: Laboratorium Sanitatis SL

6.2 Comparator (Blinded)

Name: NFX88 Placebo

Active ingredient: N/A

Pharmaceutical form: Coated tablet

Posology: three times a day (at meal times: breakfast, lunch and dinner)

Presentation: Triflex (PP/AL/PVC/PVDC)/Aluminium unit dose blisters containing 12 x 1 tablet

Excipients dose: 1200 mg + 4% of coating approx..

Manufactured by: Laboratorium Sanitatis SL

6.3 Method of Assigning Subjects to Treatment Groups

Up to 60 completed patients.

All eligible patients, who fulfil all inclusion criteria and do not meet any exclusion criteria, will be randomly assigned to NFX88 arms or placebo treatment groups in a 1:1:1:1 ratio. A centralized randomisation list will be generated in order to assign active treatment or placebo to 1, 2, 3 or 4 arms of the study as specified here.

- To ensure the 1:1:1:1 distribution of the up to 60 completed patients we will use block randomisation. The randomisation will be by blocks multiples of 4 (so 4, 8 12...) but the size of the blocks will be kept secret by the Data Manager (DM). This will minimise the chances of anyone involved in the study of guessing the allocation of a next patient. In the final report the details of the randomisation procedure will be revealed.
- To ensure blinding we will follow a central allocation procedure: A randomisation lists will be generated by the DM and incorporated into the electronic data management system. When a new patient is recruited, the system will pull the next allocation in the

randomisation list and will communicate the Site investigator what steps to follow. In this way, the allocation remains blinded to the patient and the Site investigator.

Patients enrolled in this study are not allowed to be randomised in this study again.

6.4 Blinding

Due to the objectives of the study, the identity of placebo and NFX88 treatment will both be blinded. Patients will be randomised to receive any of them in a double-blind model such that neither the investigator nor the patient will know which combination is being administered. There is no known protocol required or laboratory procedures that would influence the integrity of the blind.

Blinding of the study medication becomes ensured as both NFX88 and Placebo packaging will be identically presented. Personal involved in conducting the study may not have access to the randomisation code before the blind is officially broken.

Study patients will be notified by informed consent form that they will receive a blind treatment, without being informed about which product (Investigational or Comparator) is being administered.

The treatment assignment will be kept separate from the study team up to database lock.

6.5 Code breaks

Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the Investigator.

Only in case of an emergency, the individual treatment code for each study patient indicating the treatment assignment will be available to the Investigator and will be revealed by opening the treatment envelope kept at the Site containing the randomisation code.

Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e., that it will alter the subject's immediate management.

The Investigator must also immediately inform the Sponsor and CRO that the code has been broken notifying the date and reason for unblinding and keeping those data recorded on the eCRF as soon as possible.

Before unblinding, the Investigator should discuss this action with the Sponsor, the study medical coordinator and the CRO, except in those cases where urgent measures have to be taken for safeguarding patients' life. Unblinding will only be granted if knowledge of the study treatment is essential for the appropriate clinical management or welfare of the patient.

When unblinding the investigator should notify the sponsor as soon as possible.

6.6 Storage Conditions

The study medication (NFX88 or Placebo) will be sent by the Sponsor directly to the Pharmacy of the investigational Sites for its storage in a key locked cupboard in a restricted

area, at a temperature always between 15 and 25°C, for its dispensation when a new patient is registered into the study.

6.7 Receiving, Dispensing and Return of Investigational Products

For each product to be administered (NFX88 or Placebo) 3 kits will be prepared per randomized patient. 1 kit per month/visit (V1, V2 and V3) will be given to patient for home administration. The kit will consist of 4 packages. Each package will contain 9 blisters; each blister with 12 tablets. The 4 packages will be named from Nº 1 to Nº 4, and each one would be content placebo or NFX88 tablets depending of the study arm the patient was to be assigned.

Study treatment administration will be performed under patient responsibility beginning on V1 until the last treatment visit (EoT), 90 days after the first treatment (visits window \pm 3 days). Three times in a daily basis, patients will take 4 tablets of investigational drug (one from each one of 4 package) with water at meals time.

Accountability of study drug will be registered on the medical history during each visit at the study Site.

Medication packages of each product will be dispensed to the patients at V1, V2 and V3; and controlled by V2, V3 and EoT or WV. In all cases, NFX88 or Placebo formulations packages will contain 432 tablets for administration throughout 30 days of treatment period.

The Site delegated staff/Pharmacy will maintain an accurate record of the shipments received by the Site and dispensing of the drug product, using a drug accountability form. An accurate drug disposition record will be kept specifying the date and amount dispensed to each subject. This inventory record must be available for monitoring/audit by the sponsor and inspection by regulatory authority at any time. Copies of this record will be provided to the sponsor at the end of the study.

The Investigator will not use any drug samples for other purposes (e.g., treating other non-study patients or deviating from the protocol regarding dose regimen, duration of treatment, etc.). The Investigator will under no circumstances give any drug samples to a third party. The Investigator agrees not to destroy any labels, empty boxes or unused drug supply without sponsor's permission.

After completion of the trial, the unused study medication will be shipped to the Sponsor or will be destroyed after authorization by the Sponsor by an authorized person according to GCP regulations.

6.8 Packaging and Labelling

All packaging operations will be performed by Laboratorium Sanitatis s.l. in accordance with Good Manufacturing Practice for Medicinal Products.

An external label will be prepared for the individual medication packages and internal labels for each dose to be administered. The label will contain the information as required by the relevant regulatory and national requirements.

Labelling will be performed according to Annex 13 of the Good Manufacturing Practice (GMP) guidelines of the European Commission (EC), ICH GCP guidelines, and local law.

6.9 Concomitant Therapy

6.9.1 Standard Therapy for Neuropathic Pain

Medical treatment with pregabalin must be maintained at the same dose (150-300 mg/day) and form of administration from the beginning until the follow-up visit (FU).

All subjects must be maintained on the same medications throughout the study period, as medically possible, without the introduction of new chronic therapies. Patients who have been treated with stable doses of neuroactive drugs (antidepressants, anticonvulsants, antispastic and similar medicines) at least during the last month prior to beginning of trial must be maintained on the same medications and the same doses throughout the study period.

All concomitant therapies will be recorded on appropriate pages of the eCRF.

6.9.2 Allowed/Additional Medications and Treatments

- Anti-inflammatory drugs are allowed to pain relief.
- Anyone considered necessary for the treatment of any concomitant disease during treatment.

6.9.3 Prohibited Medications and Treatments

The opiates (major and minor) and cannabinoids (synthetic, natural or analogous) are prohibited during the study and their administration will be considered a protocol violation.

6.9.4 Maintenance Medication

Patients would continue the usual therapy with pregabalin, until the follow-up visit. Investigators will offer the best therapeutic option after patients end trial participation. Decisions regarding treatment will be a consensus between investigator and patient

7. STUDY PROCEDURES AND GUIDELINES

7.1 Clinical Assessments

Prior to conducting any study-related activities, written informed consent must be signed and dated by the subject and the investigator or designee.

Patients should be closely monitored for the onset of related evidence of severe reactions.

A schedule of events representing the required testing procedures to be performed for the duration of the study is summarized in Table 1 and explained in the following sections.

7.1.1 Concomitant Medications

All concomitant medication will be documented at Screening Visit (SV), at visits: V1, V2, V3, end of treatment (EoT) and follow-up (FU) visits, and when applicable at withdrawal visit (WV).

7.1.2 Demographics

Demographic information (date of birth, sex, race, weight), alcohol and smoking habits will be recorded at Screening.

7.1.3 Medical History

Relevant medical history, including history of primary diagnosis and neuropathic pain, previous medication received and information regarding underlying diseases will be recorded.

7.1.4 Neurological Examination

To verify the patient's diagnosis, a neurological examination will be performed and recorded in the ASIA scale according with the International Standards for Neurological and Functional Classification (ISNSCI), which establishes a classification according to 5 degrees determined by the absence or preservation of motor and sensory function, indicating the severity of injury. See Annex 1.

7.1.5 Vital Signs

Body temperature, blood pressure and pulse rate will be performed after resting for 5 minutes.

7.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the (eCRF).

7.2 Clinical Laboratory Measurements

Approximately 10 mL of blood and urine will be collected for each clinical laboratory evaluation (haematology, clinical chemistry and urinalysis). These samples will be taken 5 times during the study, for a total of approximately 50 mL collected throughout the study for each patient.

7.2.1 Haematology

Blood will be obtained and sent to each site's clinical haematology laboratory for a complete blood count (haemoglobin, haematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count), erythrocyte sedimentation rate (ESR), and mean corpuscular volume (MCV).

7.2.2 Clinical Chemistry

Blood will be obtained and sent to each Site's clinical chemistry laboratory for determination of serum glucose, urea, creatinine, sodium, potassium, chloride, calcium, phosphorus, Protein (total), albumin, cholesterol, triglycerides, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma-glutamyl transferase (GGT), alkaline phosphatase and high-density lipoprotein (HDL).

The physician in charge or designee will assess each routine laboratory abnormal value to determine if it is clinically significant. For the patients included in the study, the laboratory values and the assessments will be documented in the study raw data and reported in the final report.

7.2.3 Urinalysis

Urine will be obtained for determination of colour, appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, creatinine.

7.2.4 Pregnancy Test

A Beta HCG serum pregnancy test will be performed from female subjects who are of childbearing age prior to their participation in the study and at EoS or WV (See Table 1). A urine pregnancy test will be made the date of randomisation to women who are of childbearing age and who, despite using a contraceptive method, have doubts about a possible pregnancy during the study treatment period.

7.3 Other tests

7.3.1 12-lead ECG

Cardiac dysfunction will be monitored by 12-lead ECGs, including assessment of QT Interval (in triplicate and ≥ 1 minute between measures)

7.4 Drug Administration Procedure

The study drugs will be taken by each subject strictly according to the protocol scheme.

Four oral doses of the assigned administration will be taken three times a day at meal times (breakfast, lunch and dinner) by the patients according to protocol scheme: patient to place NFX88 or placebo tablets directly from the blister onto their mouth and swallowed one after the other, with water until completing the 4 doses. Every tablet must be swallowed whole and must not be chewed or broken.

7.5 Other Safety Measurements

Extension of the cephalic sensory deficit and increased spasticity might mean a worsening of the neurological deficit. Non-worsening of spasticity and motor score will be obtaining as the non-increase of the scales values MAS (Annex 2) and ASIA (Annex 1), respectively, from the beginning to the end of the treatment.

- **Modified Ashworth Scale (MAS):** This tool is completed by the physician. MAS tests resistance during passive soft-tissue stretching and is used as a simple measure of spasticity. The physician asks the patient to move a limb though its full range of movement and scores the patient according to the following scale. Scores range from 0-4, with 6 choices (0, 1, 1+, 2, 3 and 4). A score of 0 indicates normal tone, and 4 indicates rigidity. See the scale in Annex 2.
- **ASIA Scale:** This tool is completed by the physician. Injuries are classified in general terms of being neurologically “complete” or “incomplete” based upon the sacral sparing definition. “Sacral Sparing” refers to the presence of sensory or motor function in the most caudal sacral segments as determined by the examination. It divides spinal cord injuries into 5 categories (A-E). A score of A indicates “Complete: No sensory or motor function is preserved in sacral segments S4-S5” and E indicates “Sensory and motor functions are normal”. A complete injury is defined as the absence of sacral sparing (i.e. sensory and motor function in the lowest sacral segments, S4-5), whereas an incomplete injury is defined as the presence of

sacral sparing (i.e. some preservation of sensory and/or motor function at S4-5). Moreover, this evaluation provides information about sensory motor level. The expected results important for safety are no changes or improvement of sensory and motor sub-scale, no changes or lowering of the neurological level and no changes or improvement of ASIA. See the scale in Annex 1.

7.6 Efficacy Measurements

The improvement in pain will be obtained from:

* the decrease in the scale values of VAS (Annex 3) and PD-Q (Annex 4) from the baseline to the end of treatment.

* the score on the PGIC scale (Annex 5) at V3, EoT or WV.

- **Visual analogue scale (VAS):** Pain intensity. Patients are asked to rate the **intensity of their pain** on average. 10-cm horizontal line presented to patients, with “no pain” as an anchor at the left end and “worst pain ever” as an anchor on the right end of the line; patients are instructed to estimate pain intensity by marking on the line the place where pain intensity falls since last week. See the scale in Annex 3.

- **Pain-DETECT (PD-Q):** The questionnaire consists of 7 questions that address the **quality of neuropathic pain** symptoms; it is completed by the patient and no physical examination is required. The first five questions ask about the **gradation of pain**, scored from 0 to 5 (never = 0, hardly noticed = 1, slightly = 2; moderately = 3, strongly = 4, very strongly = 5). Question 6 asks about the **pain course pattern**, scored from -1 to 2, depending on which pain course pattern diagram is selected. Question 7 asks about **radiating pain**, answered as yes or no, and scored as 2 or 0 respectively. The final score between 1 and 38, indicates the likelihood of a neuropathic pain component. A score of ≤ 12 indicates that pain is unlikely to have a neuropathic component ($< 15\%$), while a score of ≥ 19 suggests that pain is likely to have a neuropathic component ($> 90\%$). A score between these values (12-19) indicates that the result is uncertain, and a more detailed examination is required to ensure a proper diagnosis. See the scale in Annex 4.

- **Patient Global Impression of Change (PGIC):** This tool is completed by the patient and evaluates from patient's perspective the improvement or worsening of his/her condition after a treatment approach has been tried. One question is used that is suited to the situation (From the beginning of treatment in this hospital until now, how would you describe the change (if any) in pain related to your post-traumatic condition?; response ranging from “Very much worse” to “Very much improved”. Score assigned by the physician range from 1 to 7: Very much improved (7), Much improved (6), Minimally improved (5), No change (4), Minimally worse (3), Much worse and Very much worse (1). See the scale in Annex 5.

7.7 Mobile Application

Patients will be closely monitored during treatment and follow-up periods of the study by means of an electronic application (app) which will work a central system management alerts to remind patients some of the trial procedures. They must use this app daily for entering data on treatment compliance. The subjects may also receive warning messages from the electronic app advising them to contact the site PI or appointed study staff, if necessary.

8. EVALUATIONS PER VISIT

8.1 Screening Visit (SV): 7 days to V1

1. Review the study and obtain written informed consent.
2. Record demographic and baseline characteristics (date of birth, sex, race, weight, alcohol and smoking habits).
3. Record a detailed medical history, including a history primary diagnosis and staging of neuropathic pain, diagnosis date, and prior treatments.
4. Females of child-bearing potential must be a negative serum pregnancy test and must be willing to practice appropriate contraceptive methods for the duration of the study (e.g. oral contraceptive, double barrier method, intra-uterine device, intra muscular contraceptive).
5. Perform neurological examination, complete the information and record scoring of ASIA scale.
6. Record scoring of MAS scale.
7. Vital signs (blood pressure, pulse rate, temperature).
8. Make sure the patient completes the information and record scoring of VAS and PD-Q questionnaires.
9. Confirm patient eligibility (inclusion/exclusion criteria).
10. Review of intercurrent illness (es), concomitant diseases.
11. Record concomitant medication.
12. Collect blood and urine for clinical laboratory test: haematology, clinical chemistry, urinalysis and pregnancy test for women of child-bearing potential.
13. Obtain a 12-lead electrocardiogram, including QT interval.
14. Perform any other examination according to investigator discretion.
15. Schedule subject for Visit 1 in 1-7 days.

8.2 Treatment period

8.2.1 Visit 1 (V1): Day 1 (± 3 days), Randomisation day and start of treatment

1. Patient eligibility confirmation.
2. Urine pregnancy test for women of child-bearing potential.
3. All male patients must take adequate contraceptive precautions during the study.
4. Vital signs (blood pressure, pulse rate, temperature).
5. Randomisation NFX88 (1.05, 2.10 and 4.20 g) vs Placebo (1:1:1:1 ratio).
6. Make sure the patient completes VAS and PD-Q questionnaire and record the scoring.
7. Record scoring of MAS and ASIA scales.

8. Review of intercurrent illness (es), concomitant diseases.
9. Concomitant medication review.
10. Assessment and recording of AEs.
11. Training session for mobile device App
12. Perform any other examination according to investigator discretion.
13. Dispensation of study drug.
14. Schedule subject for Visit 2 in 30 days.

8.2.2 Visit 2 (V2): Day 30 (± 3 days)

1. Vital signs (blood pressure, pulse rate, temperature).
2. Collect blood and urine for clinical laboratory test: urinalysis, haematology and clinical chemistry.
3. Make sure the patient completes VAS and PD-Q questionnaire and record the scoring.
4. Record scoring of MAS and ASIA scales.
5. Obtain a 12-lead electrocardiogram, including QT interval.
6. Dispensation and accountability of study drug.
7. Review subject dosing compliance.
8. Review of intercurrent illness(es), concomitant diseases.
9. Record changes to concomitant medications.
10. Record any Adverse Events.
11. Perform any other examination according to investigator discretion.
12. Schedule subject for Visit 3 in 60 days from V1.

8.2.3 Visit 3 (V3): Day 60 (± 3 days)

1. Vital signs (blood pressure, pulse rate, temperature).
2. Collect blood and urine for clinical laboratory test: urinalysis, haematology and clinical chemistry.
3. Make sure the patient completes VAS, PD-Q and PGIC questionnaires and record the scoring.
4. Record scoring of MAS and ASIA scales.
5. Obtain a 12-lead electrocardiogram, including QT interval.
6. Dispensation and accountability of study drug.
7. Review subject dosing compliance.
8. Review of intercurrent illness (es), concomitant diseases.
9. Record changes to concomitant medications.

10. Record any Adverse Events.
11. Perform any other examination according to investigator discretion.
12. Schedule subject for Visit 4 in 90 days from V1.

8.2.4 Visit 4 (EoT): Day 90 (± 3 days), end of treatment

1. Vital signs (blood pressure, pulse rate, temperature).
2. Collect blood and urine for clinical laboratory test: urinalysis, haematology and clinical chemistry.
3. Make sure the patient completes VAS, PD-Q and PGIC questionnaires and record the scoring.
4. Record scoring of MAS and ASIA scales.
5. Obtain a 12-lead electrocardiogram, including QT interval.
6. Accountability of study drug.
7. Review subject dosing compliance.
8. Review of intercurrent illness(es), concomitant diseases.
9. Record changes to concomitant medications.
10. Record any Adverse Events.
11. Perform any other examination according to investigator discretion.
12. Schedule subject for Follow-up visit in 120 days from V1.

8.3 Post Treatment Period

8.3.1 Visit 5 (EoS/FU): Day 120 (± 3 days), end of study or follow up visit

For those patients who complete the treatment period and perform Follow-Up visit as per protocol, the Follow-Up visit will be considered the End of Study visit.

1. Vital signs (blood pressure, pulse rate, temperature).
2. Collect blood and urine for clinical laboratory test: urinalysis, haematology, clinical chemistry and pregnancy test for women of child-bearing potential
3. Make sure the patient completes VAS and PD-Q questionnaire and record the scoring.
4. Record scoring of MAS and ASIA scales.
5. Obtain a 12-lead electrocardiogram, including QT interval.
6. Review of intercurrent illness(es), concomitant diseases.
7. Record changes to concomitant medications.
8. Record Adverse Events (only those open or new due to an AE related or suspected to be related to study drug).
9. Females of child-bearing potential must be a negative serum pregnancy test.
10. Perform any other examination according to investigator discretion.

8.3.2 Withdrawal Visit (see reasons for withdrawal in section 5)

Those patients that are withdrawn before completing the treatment period or follow-up period will need to perform a visit, which should be scheduled once this decision is taken. Whenever feasible the following assessments should be done for withdrawn patients:

1. Vital signs (blood pressure, pulse rate, temperature).
2. Collect blood and urine for clinical laboratory test: urinalysis, haematology, clinical chemistry and pregnancy test for women of child-bearing potential.
3. Make sure the patient completes VAS, PD-Q and PGIC questionnaires and record the scoring.
4. Record scoring of MAS and ASIA scales.
5. Obtain a 12-lead electrocardiogram, including QT interval.
6. Accountability of study drug.
7. Review subject dosing compliance.
8. Review of intercurrent illness(es), concomitant diseases.
9. Record changes to concomitant medications.
10. Record any Adverse Events.
11. Females of child-bearing potential must be a negative serum pregnancy test.
12. Perform any other examination according to investigator discretion.

9. SAFETY ASSESSMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

9.1 Safety Parameters

9.1.1 Definition of adverse events

An adverse event (AE) is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AE only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or haematological stem cell support), or require changes in study medication(s).

Except for screening failures, AE that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical Record and eCRF. AE monitoring should be continued for at least 30 days following the last dose of study treatment. AE (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever

possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

AE will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the End of Treatment or Study Completions Forms.

The occurrence of AE should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events may also be detected when they are reported by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy).
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 19.1.3.
- All AE should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

9.1.2 Laboratory test abnormalities

Abnormal results will be verified to rule out laboratory error. Laboratory abnormalities that constitute an AE in their own right (because are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anaemia instead of low haemoglobin). Laboratory abnormalities that meet the criteria for AE should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory /test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AE.

9.1.3 Definition of serious adverse events

Serious adverse event (SAE) is defined as one of the following:

- It is fatal or life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability/incapacity
- It constitutes a congenital anomaly/birth defect
- It is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to Neurofix s.l. or designee (QualitecFarma s.l.).

9.1.4 Definition of adverse events of special interest (AESI)

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to Sponsor. An AESI may be serious or non-serious. The quick reporting of AESIs allows ongoing analysis of these events to characterize and understand them in association with the use of this investigational product.

NFX88 has confirmed an excellent pattern of safety and tolerability with no relevant adverse event observed at any administered dose in previous Phase I studies conducted. In that study, some gastrointestinal symptoms appeared in doses of 16 g per day (which could be the result of the large amount of excipients, mainly mannitol). However, provided that in this study, the amounts of API and excipients will be lower than those used in the previous study, the company does not include the monitoring of AESIs.

However, considering that gastrointestinal symptoms has appeared in one of the previous studies with NFX88, sponsor contemplates to closely monitor the occurrence of this symptom during the present study in order to obtain more information on NFX88 safety profile and its relationship with the appearance of gastrointestinal symptoms.

9.2 Assessment of safety parameters

9.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0.

The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1-5 as defined below:

ADVERSE EVENTS SEVERITY GRADING SCALE	
GRADE	SEVERITY
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate: minimal, local, or non-invasive intervention indicate; or limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living
4	Life-threatening consequences or urgently intervention indicated
5	Death related to adverse event

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the above criteria. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

9.2.2 Assessment of relationship

Assessment of relationship to either investigational product or study procedures will be made by investigator.

9.3 Documentation and Reporting of Adverse Events

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible aetiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to Neurofix s.l. or designee (QualitecFarma s.l.).

The following variables will be collected at least for each AE:

- AE (verbatim)
- The date <>and time<> when the AE started and stopped
- Changes in NCI CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against NFX88 (yes or no)
- Action taken regarding NFX88 or placebo treatment
- Outcome

Patients will be questioned on their health status in each study visit before departing from the clinical Site. Open-ended questions will be asked. Out of those occasions, patients will have opportunity to contact the investigator to report any adverse event taking place.

Classification will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or higher.

9.4 Serious Adverse Event Reporting Requirements and Documentation

For patients who sign the main study ICF, SAE collection starts at the time of main study informed consent whether the patient is a screening failure or not. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Neurofix s.l. or designee (QualitecFarma s.l.) within 24 hours of learning of its occurrence. Any SAEs experienced after this 30-day period should be only reported to Neurofix s.l. or designee (QualitecFarma s.l.) if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported to Neurofix s.l. or QualitecFarma s.l. as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Reporting Form (see SAE Reporting Manual/QualitecFarma's SOP). This includes SAE observed in the investigational drug group and in the placebo group (e.g., reference). This notification will contain a description of the observed symptoms and an assessment of causality. A detailed report will be sent in the following days containing, in addition the information below:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

The investigator must assess and record the relationship of each SAE to the study treatment in source documents and CRF, complete the SAE Report Form in English, and send the completed, signed form by email or fax within 24 hours to the responsible person in Neurofix s.l. or designee (QualitecFarma s.l.).

The contact data of responsible personnel for pharmacovigilance in QualitecFarma s.l. is listed below:

Laura Florez / M^a Eugenia Díaz

Phone: (+34) 913 728 399 / 400
email: drug.safety@qualitecfarma.com

The original copy of the SAE Report Form and the e-mail confirmation must be kept with the CRF documentation at the study Site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

A SAE will be considered as "unexpected" when the nature or severity is not consistent with information in the relevant source document(s). The sponsor or designee is responsible for assessing whether the SAE is expected or not.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the Neurofix's study treatment, Neurofix s.l. or designee (QualitecFarma s.l.) with advice of the medical advisory board may urgently require further information from the investigator for deciding on meeting requirements for expedited report to the AEMPS. Neurofix s.l. or designee (QualitecFarma s.l.) may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSAR) will be collected and reported to the competent authorities in accordance with Regulation (EU) No 536/2014 and national regulatory requirements in Spain (RD 1090/2015).

9.4.1 Reporting of deaths

All deaths that occur during the study or within the protocol-defined 30-day post-last-dose of NFX88 safety follow-up period must be reported as follows:

1. Death that is clearly the result of disease progression should be documented but should not be reported as a SAE.
2. Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
3. Deaths with an unknown cause should always be reported as a SAE. An autopsy maybe helpful in the assessment of the cause of death, and if performed an anonymized copy of the autopsy results should be forwarded to Neurofix s.l. or designee (QualitecFarma s.l.) within the usual timeframes.
4. Deaths that occur following the protocol-defined 30-day post-last-dose of NFX88 treatment safety follow-up period will be documented "as events for survival analysis" but will not be reported as an SAE.

9.4.2 Other Events Requiring Reporting

Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Patients should be trained to notify the Investigator as soon as possible if they became pregnant during any phase of the study or immediately following the end of the study.

The investigator or designee will record pregnancy on a Pregnancy Report Form and report Neurofix s.l. or designee (QualitecFarma s.l.) within 24 hours of the knowledge of its occurrence. Because of the possibility that the foetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or new-born complications.

Women of child-bearing potential

Women who are not postmenopausal (at least 12 months) or surgically sterile must have a negative serum pregnancy test at screening and at the end of study or WV. Furthermore, they must have a negative urine pregnancy test at randomisation.

Women of child-bearing potential must agree to use a highly effective method of birth control or to abstain from sexual intercourse for the duration of the study and after 12 weeks after the last dose of study drug.

Male subject's partners pregnancy

Men patients must agree to use effective contraception or remain abstinent, and refrain from donating sperm for the duration of the study and after 12 weeks after the last dose of study drug.

Male patients should be instructed to notify the Investigator if it is determined that during the study or after completion of the study that their partner became pregnant during the treatment phase of the study.

Whenever possible any pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to the Neurofix s.l. or designee (QualitecFarma s.l.) after delivery.

9.5 Study Recording Period and Follow-Up for AEs and SAEs

For the purposes of this study, the period of observation of clinical events extends from the signed ICF until 30 days after the last administration of the study drug. During this period, all clinical events spontaneously reported by the subject, observed by the clinical staff or obtained by general questioning will be recorded on a AE form sheet reported in the eCRF.

During the study, all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

9.5.1 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study will be followed up by the investigator if medically indicated, but without further recording in the eCRF. After 30 days, only patients with ongoing investigational product-related SAEs will continue to be followed for safety. Neurofix s.l. or designee (QualitecFarma s.l.) retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) until the end of the study, if judged necessary.

10. STATISTICAL METHODS

(A separate Statistical Analysis Protocol is developed for this trial. Here we describe the main methods that will be used for the statistical analysis).

10.1 Variable examination and baseline comparisons.

A descriptive analysis of baseline variables and descriptive comparisons in the four trial arms will be performed. No inference tests are needed at baseline as this is a randomized study. Categorical variables will be described with proportions and continuous variables will be described with means, standard deviations, medians and quartiles to examine their possible non-symmetrical distribution. Key continuous outcome variables will be examined for skewness and outliers, and suitable transformations (such as logarithms and roots) will be tried if needed to normalize the variable.

10.2 Safety Assessment (Main Objective)

Sample: The safety population will include all patients who were randomised, including those that withdrew for any reasons.

Coding: For the analysis, each adverse event (AE) will be coded as a binary variable (Present/Absent) in each study subject. AEs defined as “unsafe levels” of some laboratory parameter or clinical biomarker will be also coded as binary. If the same AE can occur at different degrees of severity several binary variables will be constructed.

Analysis: Tables with counts and proportions of each AE in each arm will be compiled. For the intervention arms, exact confidence intervals for the proportion of each AE will be estimated. Comparison of the risk of each EA between arms will be done with Fisher's exact tests. To increase power, the patients from the three intervention doses will be analysed together in one intervention arm. If some AE turned out to be relatively common, a logistic regression model will be built to examine if there is a dose-response effect on the probability of such adverse event.

10.3 Efficacy Assessment (Secondary Objective)

Sample: The efficacy analysis will include all patients who were randomised, had at least 75% of treatment compliance and completed the appropriate questionnaires of VAS, PD-Q and PGIC.

Coding: The efficacy variable VAS will be coded as a continuous variable. It cannot have outliers as is limited between 0 and 10 by construction. PD-Q will be coded as continuous (from 0 to 38) but also a categorical variable with categories (<12, 12-19 and >10) as explained in section 7.5 and annex 4). PGIC will be coded as a categorical.

Analysis: The efficacy variables VAS will be analysed with a regression model to evaluate if changes from baseline (V1) to the last available questionnaire (ideally EOT) depend on treatment, while adjusting for baseline to account for the possible “regression to the mean” effect [Senn SS, 2007]. If there are large imbalances of times between the two questionnaires between the trial arms, we will adjust the models for this covariate. Model's residuals will be checked visually and through normality tests. Separate models will be built using the original scale of the variable and its log-transformation, to study the possible proportional effect of the intervention. PD-Q will be analysed in an analogous way as VAS as a continuous variable. However, we will also analyse PD-Q as a categorical variable with a multinomial regression to evaluate if the probability of having a neuropathic component of the pain depends on treatment. PGIC will be analysed as a categorical variable with multinomial logistic regression (recoding in three categories: worsening, no change and improvement due to the small sample size). All analyses will be done twice: first using the treatment variable as binary (placebo/intervention) and then coding the treatment into four categories of doses (where placebo arm has dose =0).

11. REGULATORY REQUIREMENTS

11.1 Liabilities

It is the Sponsor's responsibility to guarantee enough insurance coverage should any serious events or deaths result directly or not from the execution of the present protocol.

11.2 Statement of Investigator

The Investigator's agreement with protocol will be signed by the site Investigator responsible for the medical decisions and care provided to the patients prior to the commencement of his responsibilities with respect to the clinical trial, as required by the Regulatory Authorities. The undertaking form will be maintained with the trial records and will be made available upon request.

11.3 Delegation of Investigator Duties

The qualified investigator will ensure that all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The qualified investigator will maintain a list of sub-investigators and other appropriately qualified professionals to whom he delegates significant trial-related duties.

The qualified investigator should delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any procedures.

11.4 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Guidelines as drawn up by the IRB/IEC will be followed with regard to the treatment of human patients in the study. These guidelines meet the requirements of the Declaration of Helsinki and Regulation (EU) No 536/2014.

This protocol and the ICF among other required documentation will be submitted to an IRB/IEC prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

Before inclusion in the study, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the patient and once the physician in charge or designee has the conviction that the patient understands the implications of participating in the study, he/she will be required to read, sign and date a properly executed written informed consent form prior to enrolment. Patients will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their informed consent form.

If an amended or revised ICF is introduced during the study, each subject's further consent should be obtained.

11.5 Case Report Form (CRF)

eCRF will be limited access by user at any time on-line in the eCRF webpage. Please review Study eCRF manual and procedures for additional information.

Corresponding Users and Passwords will be provided once Site is activated and has received applicable training.

Once all eCRF are completed and reviewed, the eCRF will be approved and signed by the Investigator.

11.6 Record Retention

All essential documents and records will be maintained at Sponsor for a period of 25 years. These documents may be retained for a longer period if needed by the Sponsor.

11.7 Quality Assurance

QualitecFarma will be responsible for maintaining an adequate study quality and quality control (QC) systems with written SOPs to ensure that the trial is conducted, and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and the applicable regulatory requirements.

The study will be conducted according to ICH E6 GCP.

11.8 Monitoring of The Study

The Sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. Sites

involved will permit trial-related monitoring visits, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11.9 Data Management and Processing

Data will be entered by the investigator in the eCRF that will feed the study database. Study investigators, trial monitor and statisticians will have access to the data with different permits according to their role and their needs, but they will be blinded to the patient's allocation. Allocation information will be saved in a restricted table of the database that will be fully revealed only after the end of the trial when the main analysis has been performed. Unblinding of a specific patient will be possible upon request of the trial investigator or the patient's physician if a SAE is detected.

The eCRF will have basic data checking possibilities and will alert of any suspected incorrect value when the data is entered. The system will also have a facility for data validation by the trial monitor. Once the trial is finalised and the dataset closed, the statisticians will proceed to do data checking for outliers and suspicious values running different statistical algorithms. If any of these are found, they will be checked back with the trial investigators and the patient's records. When all these issues are solved, a final data set for analysis will be saved and closed. On this data, the statistician will proceed to run the different analysis for main and secondary outcomes.

At all times, the system will keep the data safe by limiting the access to authorise personnel with appropriate security restrictions such as passwords and encryption. The system will comply with data security regulations of the European Union and Spain.

11.10 Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, Sponsor, CRO or the qualified investigator should promptly inform the trial patients, should assure appropriate therapy and follow-up for the patients and, where required by the applicable regulatory requirement(s), should inform the Regulatory Authority(ies). All procedures should be done according to defined SOPs.

11.11 Adherence to Protocol

Excluding an emergency in which proper treatment is required for the protection, safety and well-being of the study patients, the study will be conducted as described in the approved protocol and performed according to ICH/GCP guidelines. Any deviation from the protocol will be recorded and explained.

If major amendments to the protocol and/or major amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB/IEC and Health Authority(ies) for approval.

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Table 1. Schedule of Study Visits

ASSESSMENTS	SCREENING VISIT	START OF TREATMENT /BASELINE	TREATMENT VISIT	TREATMENT VISIT	END OF TREATMENT	FOLLOW-UP VISIT/END OF STUDY	WITHDRAWAL VISIT
	SV	V1	V2	V3	V4/EOT	V5/FU/EOS	WV
	D -7	D 1 ^a	D 30 ^a	D 60 ^a	D 90 ^a	D 120 ^a	
Informed Consent	X						
Inclusion/exclusion criteria	X	X					
Randomisation		X					
Medical History	X						
Demographic, alcohol and smoking habits	X						
Neurological Examination (ASIA scale)	X	X	X	X	X	X	X
VAS questionnaire	X	X	X	X	X	X	X
Vital signs (temperature, blood pressure, pulse rate)	X	X	X	X	X	X	X
Urinalysis, Haematology and chemistry sample collection	X		X	X	X	X	X
Pregnancy test sample collection (blood)	X(b)	X(u)				X(b)	X(b)
12-lead ECG, QT interval	X		X	X	X	X	X
PD-Q questionnaires	X	X	X	X	X	X	X
MAS scale	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
Intercurrent illness (es), concomitant diseases.	X	X	X	X	X	X	X
Drug Dispensation		X	X	X			
Drug accountability			X	X	X		X
Subject dosing compliance			X	X	X		X
PGIC questionnaire				X	X		X
Training session for mobile device App		X					
Other Examination	X	X	X	X	X	X	X

^a ±3 days

u: Urine

b: Blood

Annex 1. ASIA-ISNSCI Scale

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY (ISNCSCI)				Patient Name _____	Date/Time of Exam _____																																																																																																																																																																																																																															
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Muscle Function Grading

- 0 = total paralysis
- 1 = palpable or visible contraction
- 2 = active movement, full range of motion (ROM) with gravity eliminated
- 3 = active movement, full ROM against gravity
- 4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position
- 5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person
- 5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present
- NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

Sensory Grading

- 0 = Absent
- 1 = Altered, either decreased/impaired sensation or hypersensitivity
- 2 = Normal
- NT = Not testable

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, abduction, adduction, internal and external rotation	C5
Elbow: Supination	
Elbow: Pronation	C6
Finger: Flexion at proximal joint, extension.	C7
Thumb: Flexion, extension and abduction in plane of thumb	
Finger: Flexion at MCP joint	C8
Thumb: Opposition, adduction and abduction perpendicular to palm	
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation	L4
Knee: Flexion	
Ankle: Inversion and eversion	
Toe: MP and IP extension	
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments (S4-S5) by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3 .

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3 .

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.

The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.

Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).

Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI)

This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.

The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.

(i.e. absence or presence of sacral sparing)

If voluntary anal contraction = No AND all S4-5 sensory scores = 0 AND deep anal pressure = No, then injury is Complete. Otherwise, injury is Incomplete.

5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If YES, AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)

Is injury Motor Complete? If YES, AIS=B

NO (No voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO **AIS=C** **YES** **AIS=D**

If sensation and motor function is normal in all segments, AIS=E

Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

ASIA
AMERICAN SPINAL INJURY ASSOCIATION
INTERNATIONAL STANDARDS FOR NEUROLOGICAL
CLASSIFICATION OF SPINAL CORD INJURY

ISCOS
INTERNATIONAL SPINAL CORD SOCIETY

Annex 2. Modified Ashworth Scale (MAS)

ESCALA DE ASHWORTH MODIFICADA			
Fecha:			
Código del paciente:			
Nombre del Centro, Ciudad:			
Espasticidad según la Escala de Ashworth: [0] [1] [1+] [2] [3] [4] marcar lo que proceda			
No hay cambios en la respuesta del músculo en los movimientos de flexión o extensión.			0
Ligero aumento en la respuesta del músculo al movimiento, solo mínima resistencia (catch).			1
Ligero aumento en la resistencia del músculo al movimiento en todo el resto del arco de movimiento.			1+
Moderado incremento en la resistencia del músculo durante la mayor parte del arco de movimiento articular, pero se puede completar el arco de movimiento.			2
Marcado incremento en la resistencia del músculo; el movimiento pasivo es difícil.			3
Las partes afectadas están rígidas cuando se mueven pasivamente.			4
	MIEMBRO SUPERIOR	MIEMBRO INFERIOR	NOTAS
DERECHA			
IZQUIERDA			

Annex 3. Visual Analogue Scale (VAS)

ESCALA VISUAL ANALÓGICA (EVA)

Fecha: _____

Código del paciente: _____

Nombre del Centro, Ciudad: _____

Marque sobre la línea, entre los dos extremos, cuánto dolor siente en esta última semana.



Firma del paciente: _____

Annex 4. PainDETECT Scale

painDETECT® CUESTIONARIO DE EVALUACION DEL DOLOR

Fecha: _____ Paciente: Nombre: _____ Apellidos: _____

¿Cómo valoraría el dolor que siente HOY, en este momento?

0	1	2	3	4	5	6	7	8	9	10
Ningún dolor										Máximo dolor

¿Cuál ha sido la intensidad del dolor **más fuerte** que ha sentido en las últimas 4 semanas?

0	1	2	3	4	5	6	7	8	9	10
Ningún dolor										Máximo dolor

¿Cuál ha sido la intensidad **MEDIA** de su dolor DURANTE las últimas 4 semanas?

0	1	2	3	4	5	6	7	8	9	10
Ningún dolor										Máximo dolor

Marque con una cruz la imagen que mejor describa el patrón de su dolor:

	Dolor constante con ligeras variaciones	<input type="checkbox"/>
	Dolor constante con crisis de dolor	<input type="checkbox"/>
	Crisis de dolor, sin dolor entre las crisis	<input type="checkbox"/>
	Crisis de dolor, con dolor entre las crisis	<input type="checkbox"/>

Marque la principal zona de su dolor

¿Se irradiia el dolor hacia otras partes de su cuerpo? sí no

Si la respuesta es sí, indique con una flecha la dirección hacia la que se irradiia el dolor.

¿Tiene una sensación de quemazón (p.ej. como por roce de ortigas) en la zona marcada?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderada <input type="checkbox"/>	intensa <input type="checkbox"/>	muy intensa <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	-----------------------------------	----------------------------------	--------------------------------------

¿Tiene una sensación de hormigueo o cosquilleo (como una corriente eléctrica) en la zona de dolor?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderada <input type="checkbox"/>	intensa <input type="checkbox"/>	muy intensa <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	-----------------------------------	----------------------------------	--------------------------------------

¿Le produce dolor cualquier ligero roce (p.ej. la ropa o las sábanas) en esta zona?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderado <input type="checkbox"/>	intenso <input type="checkbox"/>	muy intenso <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	-----------------------------------	----------------------------------	--------------------------------------

¿En la zona de dolor marcada, tiene crisis de dolor repentina, como descargas eléctricas?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderados <input type="checkbox"/>	intensos <input type="checkbox"/>	muy intensos <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	------------------------------------	-----------------------------------	---------------------------------------

¿En la zona del dolor, en alguna ocasión le produce dolor el contacto del frío o el calor (p.ej. el agua de la ducha)?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderado <input type="checkbox"/>	intenso <input type="checkbox"/>	muy intenso <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	-----------------------------------	----------------------------------	--------------------------------------

¿Tiene una sensación de entumecimiento en la zona de dolor marcada?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderada <input type="checkbox"/>	intensa <input type="checkbox"/>	muy intensa <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	-----------------------------------	----------------------------------	--------------------------------------

¿Se desencadena el dolor con solo una ligera presión en la zona de dolor marcada (p. ej. con el dedo)?

no <input type="checkbox"/>	Muy ligera <input type="checkbox"/>	Ligera <input type="checkbox"/>	moderado <input type="checkbox"/>	intenso <input type="checkbox"/>	muy intenso <input type="checkbox"/>
-----------------------------	-------------------------------------	---------------------------------	-----------------------------------	----------------------------------	--------------------------------------

(a llenar por el médico)

nunca	Muy ligera	Ligera	moderada	intensa	muy intensa
<input type="checkbox"/> x 0 = 0	<input type="checkbox"/> x 1 =	<input type="checkbox"/> x 2 =	<input type="checkbox"/> x 3 =	<input type="checkbox"/> x 4 =	<input type="checkbox"/> x 5 =

Puntuación total _____ sobre 35

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painDETECT® Puntuación del Cuestionario de evaluación del dolor

Fecha: _____ Paciente: Nombre: _____ Apellidos: _____

Transcriba la puntuación total del cuestionario de evaluación del dolor:
Puntuación total

Añada a la puntuación anterior las siguientes cifras en función del patrón de dolor marcado y de la presencia o ausencia de dolor irradiado. A continuación calcule la puntuación final:

	Dolor constante con ligeras variaciones	<input type="text" value="0"/>	
	Dolor constante con crisis de dolor	<input type="text" value="-1"/>	si se ha marcado esta imagen, o
	Crisis de dolor, sin dolor entre las crisis	<input type="text" value="+1"/>	si se ha marcado esta imagen, o
	Crisis de dolor, con dolor entre las crisis	<input type="text" value="+1"/>	si se ha marcado esta imagen
	¿Dolor irradiado?	<input type="text" value="+2"/>	si la respuesta es sí

Puntuación final

Resultado del análisis
de la presencia de un componente de dolor neuropático

negativo	dudoso	positivo
0 1 2 3 4 5 6 7 8 9 10 11	12 13 14 15 16 17 18	19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38
No es probable que exista un componente de dolor neuropático (< 15%)	El resultado es ambiguo, pero puede existir un componente de dolor neuropático	Es probable que exista un componente de dolor neuropático (> 90%)

Este cuestionario no sustituye el diagnóstico médico.
 Se utiliza para analizar la presencia de un componente de dolor neuropático.

DFNS

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Annex 5. Patient Global Impression of Change (PGIC) Scale**ESCALA DE IMPRESIÓN DEL CAMBIO GLOBAL DEL PACIENTE**

Fecha:

Código del paciente:

Nombre del Centro, Ciudad:

Desde el comienzo del tratamiento en este hospital hasta ahora, ¿cómo describiría el cambio (si existe) en el dolor relacionado con su condición post traumática?

Marque con una (X) una sola respuesta.

Gran mejoría	<input type="checkbox"/>
Mejoría	<input type="checkbox"/>
Leve mejoría	<input type="checkbox"/>
Sin cambio	<input type="checkbox"/>
Leve empeoramiento	<input type="checkbox"/>
Empeoramiento	<input type="checkbox"/>
Gran empeoramiento	<input type="checkbox"/>

Firma del paciente:
