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.
STUDY CODE	NFX88-2A-2018
SPONSOR	Neurofix S.L.
CRO	QualitecFarma, S.L.
SYNOPSIS VERSION	V1.0 28Dec2018
EudraCT Nº	2018-004792-13
NUMBER OF SITES	4 National sites have been pre-selected
CLINICAL PHASE	IIa (proof of concept)
STUDY DESIGN	Multicentric, Randomized, Double Blind, Parallel Group (NFX88 vs Placebo-Controlled) Clinical Trial
STUDY TYPE	Interventional
STUDY POPULATION	Spinal cord injury patients with neuropathic pain
ANTICIPATED START DATE	Q2 2019 (Jun 2019)
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	**Recruitment Phase**: ~6 months **Completion of Recruitment**: Q3 2019 (Dec 2020) Subjects will be on study for up to 127 days **Screening:** up to 1-7 days **Treatment:** 90 days **Follow-up:** 30 days The total duration of the study is expected to be 1 year and 6 months
TOTAL NUMBER OF SITES	4 sites have been pre-selected Competitive recruitment
CEIm	Comité de Ética de Investigación con medicamentos Regional (CEIm-R) de la Comunidad de Madrid
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/II 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.
PRIMARY OBJECTIVE	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.
SECONDARY OBJECTIVES	The trial will also explore the preliminary therapeutic efficacy associated with NFX88 through the analysis of validated measurement scales (VAS, PD-Q, PGIC)
PLANNED SAMPLE SIZE	**Total**: up to 60 completed patients **A. Experimental Arm** 1) 1.05 g/day NFX88: 15 patients. 2) 2.10 g/day NFX88: 15 patients. 3) 4.20 g/day NFX88: 15 patients. **B. Control Arm** 1) Placebo: 15 patients.
SUBJECT SELECTION CRITERIA	**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 50-115 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**: 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 tablets. 11. History of cancer except local basal or squamous cell carcinoma of the skin that has been excised
EXPERIMENTAL DRUG	NFX88 Pharmaceutical form: coated tablets Strength: 350 mg
CONTROL DRUG	Placebo Pharmaceutical form: coated tablets Strength: 0 mg
DOSING REGIMEN AND TREATMENT SCHEDULE	**Doses**: **A. Experimental Arms**

	a. 1.05 g/day NFX88 b. 2.10 g/day NFX88 c. 4.20 g/day NFX88 **B. Control Arm** a. 0.00 g/day Placebo coated tablets **Frequency**: 3 times a day (t.i.d.) **Duration of the treatment**: 90 days **Total duration of the trial:** 1-7 Screening days, 90 treatment days (approximately 3 months) and 30 Follow-up days
CONCOMMITANT MEDICATIONS	**Allowed**: - Anti-inflammatory drugs are allowed to pain relief - Anyone considered necessary for the treatment of any concomitant disease during treatment **Prohibited**: 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.
EFFICACY EVALUATIONS	Effect of NFX88 in changes of neuropathic pain reduction scales: - 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)
PRIMARY ENDPOINT	**Safety and tolerability:** - Incidence of serious adverse events - Incidence of severity 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 ENDPOINTS	**Efficacy:** - Improvement in neuropathic pain scales VAS, PD-Q, and PGIC
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	Safety and tolerability of NFX88 administered for 90 days will be assessed by the number, severity, and type of AE, including changes in: - Vital signs (Time Frame: SV, 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).
PLANNED INTERIM ANALYSES (if applicable)	N/A
STATISTICS	The planned analysis for the primary and secondary endpoints will be done when the last patient has completed treatment period. For more details, please see Study Protocol and Statistical Analysis Plan.
Rationale for Number of Subjects	The number of subjects for the study has not been formally calculated. Please, refer to the Statistical Analysis Plan.