



## Clinical trial results:

**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.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2018-004792-13 |
| Trial protocol           | ES             |
| Global end of trial date | 12 April 2022  |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 20 May 2023   |
| First version publication date    | 20 May 2023   |
| Summary attachment (see zip file) | Protocol Synopsis (NFX-88 Protocol Synopsis V1.0 28Dec2018 English FINAL.pdf) |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | NFX88-2A-2018 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Neurofixpharma   |
| Sponsor organisation address | Calle del Adaja, 3 Parque Científico de la Universidad de Salamanca Edificio M3 PB05 Sala 1, Salamanca, Spain, 37185 |
| Public contact               | Miguel Angel Ávila Santiago, Neurofixpharma S.A., 0034 674052566, miguelangel.avila@neurofixpharma.com               |
| Scientific contact           | Miguel Angel Ávila Santiago, Neurofixpharma S.A., 0034 674052566, miguelangel.avila@neurofixpharma.com               |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 29 November 2022 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 12 April 2022    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 12 April 2022    |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

Treated in routine care

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 June 2019     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 1 Months         |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 61 |
| Worldwide total number of subjects   | 61        |
| EEA total number of subjects         | 61        |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 56 |
| From 65 to 84 years                       | 5  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment phase: ~18 months

60 patients to be recruited in 4 arms

### Pre-assignment

Screening details:

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.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 61 |
| Number of subjects completed | 61 |

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Randomization (overall period)               |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

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.

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | ARM 1: 1.05 g/day |

Arm description:

1.05 g/day NFX88

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | NFX88        |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

1.05 g/day oral use

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | ARM 2. 2.1g/day NFX88 |
|------------------|-----------------------|

Arm description:

2.10 g/day NFX88

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | NFX88             |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

2.10 g/day ORAL USE

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | ARM 3: 4.2 g/day |
|------------------|------------------|

Arm description:

4.20 g/day NFX8

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | NFX88             |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

4.20 g/day ORAL USE

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | ARM 4: 0.0 g/day |
|------------------|------------------|

Arm description:

PLACEBO

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | PLACEBO  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

ORAL USE

| <b>Number of subjects in period 1</b> | ARM 1: 1.05 g/day | ARM 2: 2.1g/day<br>NFX88 | ARM 3: 4.2 g/day |
|---------------------------------------|-------------------|--------------------------|------------------|
| Started                               | 15                | 15                       | 16               |
| Completed                             | 12                | 11                       | 12               |
| Not completed                         | 3                 | 4                        | 4                |
| Consent withdrawn by subject          | 1                 | -                        | 1                |
| Physician decision                    | -                 | 2                        | -                |
| Adverse event, non-fatal              | 1                 | 1                        | 2                |
| Lost to follow-up                     | 1                 | -                        | -                |
| Protocol deviation                    | -                 | 1                        | 1                |

| <b>Number of subjects in period 1</b> | ARM 4: 0.0 g/day |
|---------------------------------------|------------------|
| Started                               | 15               |
| Completed                             | 9                |
| Not completed                         | 6                |
| Consent withdrawn by subject          | 1                |
| Physician decision                    | -                |

|                          |   |
|--------------------------|---|
| Adverse event, non-fatal | 1 |
| Lost to follow-up        | - |
| Protocol deviation       | 4 |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Randomization |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values                             | Randomization | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 61            | 61    |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero   |               | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) |               | 0     |  |
| Newborns (0-27 days)                               |               | 0     |  |
| Infants and toddlers (28 days-23 months)           |               | 0     |  |
| Children (2-11 years)                              |               | 0     |  |
| Adolescents (12-17 years)                          |               | 0     |  |
| Adults (18-64 years)                               |               | 0     |  |
| From 65-84 years                                   |               | 0     |  |
| 85 years and over                                  |               | 0     |  |
| Age continuous                                     |               |       |  |
| Male or Female 18 to 65 years of age               |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 47.2          |       |  |
| full range (min-max)                               | 22 to 67      | -     |  |
| Gender categorical                                 |               |       |  |
| Male or Female 18 to 65 years of age               |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 12            | 12    |  |
| Male   | 49            | 49    |  |

## End points

### End points reporting groups

|                              |                       |
|------------------------------|-----------------------|
| Reporting group title        | ARM 1: 1.05 g/day     |
| Reporting group description: |                       |
| 1.05 g/day NFX88             |                       |
| Reporting group title        | ARM 2: 2.1g/day NFX88 |
| Reporting group description: |                       |
| 2.10 g/day NFX88             |                       |
| Reporting group title        | ARM 3: 4.2 g/day      |
| Reporting group description: |                       |
| 4.20 g/day NFX8              |                       |
| Reporting group title        | ARM 4: 0.0 g/day      |
| Reporting group description: |                       |
| PLACEBO                      |                       |

### Primary: Safety and tolerability of NFX88 administered by 90 days

|   |  |
|---|--|
| End point title   | Safety and tolerability of NFX88 administered by 90 days |
| End point description:  |  |
| Safety and tolerability of NFX88 administered for ninety days will be evaluated by assessing the number, severity, and type of Adverse Event, including changes in vital signs, safety laboratory values (haematology, clinical chemistry and urinalysis), ECGs, and MAS (Modified Ashworth Scale) (e.g. to monitor spasticity worsening) and ASIA (e.g. to monitor neurological worsening) scores. |  |
| Non-worsening of spasticity and motor score will be obtaining as the non-increase of the scales values MAS and ASIA, respectively, from the beginning to the end of the treatment.  |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Safety and tolerability of NFX88 administered for 3 months will be assessed by the number, severity, and type of Adverse Events from screening visit (-7 days) to the Follow up visit (120 days after the start of the treatment)   |  |

| End point values            | ARM 1: 1.05 g/day | ARM 2: 2.1g/day | ARM 3: 4.2 g/day | ARM 4: 0.0 g/day |
|-----------------------------|-------------------|-----------------|------------------|------------------|
| Subject group type          | Reporting group   | Reporting group | Reporting group  | Reporting group  |
| Number of subjects analysed | 15                | 15              | 16               | 15               |
| Units: Adverse Events       |                   |                 |                  |                  |
| Severe                      | 1                 | 2               | 3                | 1                |
| Mild                        | 14                | 4               | 18               | 14               |
| Moderate                    | 1                 | 0               | 3                | 1                |

### Statistical analyses

|                            |                 |
|----------------------------|-----------------|
| Statistical analysis title | Safety analysis |
|----------------------------|-----------------|

Statistical analysis description:

CODING: For the analysis, each adverse event (AE) was coded as a binary variable (Present/Absent) in

each study subject. AEs defined as “unsafe levels” of some lab parameter or clinical outcome (vital signs, ECGs, ASIA and MAS scales) were also coded as binary. If the same AE occur at different degrees of severity several binary variables were calculated

|   |   |
|---|---|
| Comparison groups                       | ARM 1: 1.05 g/day v ARM 2. 2.1g/day NFX88 v ARM 3: 4.2 g/day v ARM 4: 0.0 g/day |
| Number of subjects included in analysis | 61  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[1]</sup>  |
| P-value                                 | ≤ 0.05  |
| Method                                  | Fisher exact  |

Notes:

[1] - Tables with counts and proportions of each AE in each arm were compiled. For the intervention arms, exact confidence intervals for the proportion of each AE were estimated. Comparison of the risk of each

EA between arms was done with Fisher’s exact tests. To increase power, the patients from the three intervention doses were analyzed together in one intervention arm. If some AE turned out to be relatively

common, a logistic regression model was built to examine if there is a dose-response ef



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety and tolerability of NFX88 administered for 90 days was assessed in the different visits: Since SV (- 7 days) to Follow-up visit (120 days after the beginning of the treatment)

Adverse event reporting additional description:

Safety and tolerability of NFX88 administered for 3 months will be assessed by the number, severity, and type of Adverse Events, including changes in:

- Vital signs.
- ECG.
- Clinical laboratory parameters
- Spasticity score as determined by MAS
- Sensory and motor function by ASIA scale

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 22.1   |

### Reporting groups

|                              |                       |
|------------------------------|-----------------------|
| Reporting group title        | ARM 1: 1.05 g/day     |
| Reporting group description: | 1.05 g/day NFX88      |
| Reporting group title        | ARM 2: 2.1g/day NFX88 |
| Reporting group description: | 2.10 g/day NFX88      |
| Reporting group title        | ARM 3: 4.2 g/day      |
| Reporting group description: | 4.20 g/day NFX8       |
| Reporting group title        | ARM 4: 0.0 g/day      |
| Reporting group description: | PLACEBO               |

| Serious adverse events                            | ARM 1: 1.05 g/day | ARM 2: 2.1g/day NFX88 | ARM 3: 4.2 g/day |
|---|-------------------|-----------------------|------------------|
| Total subjects affected by serious adverse events |                   |                       |                  |
| subjects affected / exposed                       | 1 / 15 (6.67%)    | 2 / 15 (13.33%)       | 1 / 16 (6.25%)   |
| number of deaths (all causes)                     | 0                 | 0                     | 0                |
| number of deaths resulting from adverse events    | 0                 | 0                     | 0                |
| Vascular disorders                                |                   |                       |                  |
| Vascular insufficiency                            |                   |                       |                  |
| subjects affected / exposed                       | 0 / 15 (0.00%)    | 1 / 15 (6.67%)        | 0 / 16 (0.00%)   |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 1                 | 0 / 0            |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0                 | 0 / 0            |
| Respiratory, thoracic and mediastinal disorders   |                   |                       |                  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Respiratory disorder                            |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 15 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 0 / 15 (0.00%) | 0 / 15 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 1 / 15 (6.67%) | 1 / 15 (6.67%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                  |  |  |
|---|------------------|--|--|
| <b>Serious adverse events</b>                     | ARM 4: 0.0 g/day |  |  |
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 1 / 15 (6.67%)   |  |  |
| number of deaths (all causes)                     | 0                |  |  |
| number of deaths resulting from adverse events    | 0                |  |  |
| Vascular disorders                                |                  |  |  |
| Vascular insufficiency                            |                  |  |  |
| subjects affected / exposed                       | 0 / 15 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Respiratory, thoracic and mediastinal disorders   |                  |  |  |
| Respiratory disorder                              |                  |  |  |
| subjects affected / exposed                       | 0 / 15 (0.00%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 0            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Renal and urinary disorders                       |                  |  |  |
| Sepsis  |                  |  |  |
| subjects affected / exposed                       | 1 / 15 (6.67%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Urinary tract infection                           |                  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 15 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | ARM 1: 1.05 g/day | ARM 2: 2.1g/day<br>NFX88 | ARM 3: 4.2 g/day |
|---|-------------------|--------------------------|------------------|
| Total subjects affected by non-serious adverse events |                   |                          |                  |
| subjects affected / exposed                           | 2 / 15 (13.33%)   | 1 / 15 (6.67%)           | 4 / 16 (25.00%)  |
| Gastrointestinal disorders                            |                   |                          |                  |
| Gastrointestinal disorder                             |                   |                          |                  |
| subjects affected / exposed                           | 1 / 15 (6.67%)    | 0 / 15 (0.00%)           | 1 / 16 (6.25%)   |
| occurrences (all)                                     | 1                 | 0                        | 1                |
| Renal and urinary disorders                           |                   |                          |                  |
| Infection   |                   |                          |                  |
| subjects affected / exposed                           | 1 / 15 (6.67%)    | 1 / 15 (6.67%)           | 3 / 16 (18.75%)  |
| occurrences (all)                                     | 1                 | 1                        | 3                |

| <b>Non-serious adverse events</b>                     | ARM 4: 0.0 g/day |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 4 / 15 (26.67%)  |  |  |
| Gastrointestinal disorders                            |                  |  |  |
| Gastrointestinal disorder                             |                  |  |  |
| subjects affected / exposed                           | 1 / 15 (6.67%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Renal and urinary disorders                           |                  |  |  |
| Infection   |                  |  |  |
| subjects affected / exposed                           | 3 / 15 (20.00%)  |  |  |
| occurrences (all)                                     | 5                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 23 May 2019      | Initial protocol v1.0 dated 28dec2018 – Conditional approval obtained on 23May2019. New version of IMPD had to be submitted and approved before study start.   |
| 29 April 2020    | Protocol v2.0 dated 13Mar2020 relevant amendment to increase the recruitment period, increase age inclusion criteria, clarify traumatic spinal cord injury meaning and specify more clearly the washout period for opioids and cannabinoids. Approved on 29Apr2020 |
| 18 November 2020 | Protocol v3.0 dated 25Sep2020 relevant amendment to include the option for home visit due to COVID pandemic. Approved on 18Nov2020   |
| 20 March 2021    | Protocol v4.0 dated 22Feb2021 relevant amendment to decrease the total number of patients to be included in the trial to 48. Approved on 20Mar2021   |
| 27 October 2021  | Protocol v5.0 dated 09Sep2021 relevant amendment to decrease the total number of patients to be included in the trial to 44. Approved on 27Oct2021   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|  |
|--|
| The recruitment and following up o the patients was slower and more complicated than usual due to the COVID pandemic situation during the years this study was carried on. |
|--|

Notes: