



Clinical trial results:

Phase I Trial of DNX-2401 for Diffuse Intrinsic Pontine Glioma newly diagnosed in pediatric patients.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2016-001577-33 |
| Trial protocol | ES |
| Global end of trial date | 24 January 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 22 May 2022 |
| First version publication date | 22 May 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | D24-DIPG |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03178032 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Clínica Universidad de Navarra |
| Sponsor organisation address | Avda. Pío XII, 36, Pamplona, Spain, 31008 |
| Public contact | UCEC, Clínica Universidad de Navarra, 34 9482554002725, ucicec@unav.es |
| Scientific contact | UCEC, Clínica Universidad de Navarra, 34 9482554002725, ucicec@unav.es |

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 | 25 January 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 January 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 January 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the safety, tolerability and toxicity of DNX-2401 injected in the cerebellar peduncle in pediatric subjects with DIPG. The trial will look for hematologic and neurologic toxicity (NCI-CTCAE v 4.03).

Protection of trial subjects:

The protection of the subjects will be in accordance with the standards of good clinical practice as well as the law of Data Protection Act

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 November 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects**Subjects enrolled per country**

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 12 |
| Worldwide total number of subjects | 12 |
| EEA total number of subjects | 12 |

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) | 10 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 1 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients will be screened in the clinic by the investigators of the trial. Screening will take place within 28 days of selection and administration of DNX-2401. Screening will be preceded by a presentation of the complete information about the clinical study to the parents

Pre-assignment

Screening details:

- Recent clinical and radiological diagnosis of DIPG.
- Physical Examination, including vital signs and weight
- Neurological Examination and Functional Status assessment
- Quality of Life instruments (PedsQLTM)
- Clinical Laboratory Tests
- Pregnancy testing
- Serology
- MRI

Period 1

| | |
|------------------------------|----------------------------|
| Period 1 title | Treatment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-----------|
| Arm title | Treatment |
|-----------|-----------|

Arm description:

DNX-2401 will be injected immediately after the biopsy.

The injection will be intratumoral through the biopsy tract in the cerebellar peduncle.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | DNX-2401 |
| Investigational medicinal product code | DNX-2401 |
| Other name | DNX-2401 |
| Pharmaceutical forms | Concentrate and solvent for solution for injection |
| Routes of administration | Intratumoral use |

Dosage and administration details:

Total dose will be D0=1x10⁹, D1=1x10¹⁰ or D2=5x10¹⁰ viral particles (vp) suspended in 1 ml for all cases. Virus will be kept in an $\leq -80^{\circ}\text{C}$ freezer, in the vial in which it was provided. Vial concentration is 2.0 x 10¹¹ vp/mL. One dilution will be required to produce the total dose for the study of 5 x 10¹⁰ vp/mL in 1.0 mL as the dose to be delivered. However, it may be necessary to prepare enough DNX-2401 in order to fill the dead space in delivery equipment in order to ensure delivery of the complete dose. The Alcyone MEMS cannula to be used in the trial has a dead volume of 50uL, and the tubing has a dead volume of 500uL. That is why a total volume of 1.6mL will be load in the syringe. The virus will be diluted and prepared in the Pharmacy of the hospital and send to the Operating Room in a syringe, ready for injection. See below the procedure for each dose: D0, D1 and D2.

| Number of subjects in period 1 | Treatment |
|--------------------------------|-----------|
| Started | 12 |
| Completed | 3 |
| Not completed | 9 |
| progression | 9 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description:

DNX-2401 will be injected immediately after the biopsy.

The injection will be intratumoral through the biopsy tract in the cerebellar peduncle.

| Reporting group values | Treatment | Total | |
|---------------------------|-----------|-------|--|
| Number of subjects | 12 | 12 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 10 | 10 | |
| Adolescents (12-17 years) | 1 | 1 | |
| Adults (18-64 years) | 1 | 1 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | 7 | |
| Male | 5 | 5 | |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | Treatment |
| Reporting group description: DNX-2401 will be injected immediately after the biopsy. The injection will be intratumoral through the biopsy tract in the cerebellar peduncle. | |

Primary: Safety, tolerability and toxicity of DNX-2401

| | |
|------------------------|--|
| End point title | Safety, tolerability and toxicity of DNX-2401 ^[1] |
| End point description: | |

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

For each individual patient the timepoint of evaluation is from the DNX.2401 injection, to the last follow up visit

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical considerations: Adverse events were described using frequencies. Kaplan-Meier methods were used to determine survival.

| | | | | |
|---------------------------------|-----------------|--|--|--|
| End point values | Treatment | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: number of adverse events | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Survival

| | |
|------------------------|----------|
| End point title | Survival |
| End point description: | |

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

For each individual patient the timepoint of evaluation was from the DNX.2401 injection to the last follow up visit

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Treatment | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Months | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between study start and Last Visit of the last patient

Adverse event reporting additional description:

None

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | D24-DIPG patients |
|-----------------------|-------------------|

Reporting group description: -

| Serious adverse events | D24-DIPG patients | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Hemiparesis (right) | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | Additional description: Sospecha de apendicitis y posterior descarte. El paciente mejoró tras su ingreso y se consideró cerrado el SAE sin relación con la medicación. | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | D24-DIPG patients | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | | |
| Vascular disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 8 / 12 (66.67%) | | |
| occurrences (all) | 10 | | |
| Irritability | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | | |
| occurrences (all) | 3 | | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | | |
| occurrences (all) | 9 | | |
| Seroma | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Ataxia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Laryngospasm | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | | |
| occurrences (all) | 3 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-----------------------|--|--|
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Psychiatric disorders Dysarthria subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 3 | | |
| Cushingoid facies subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 3 | | |
| Injury, poisoning and procedural complications Wound complication subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Incision site pain subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Nervous system disorders Worsening of previous instability subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Neurological decompensation subjects affected / exposed occurrences (all) | 8 / 12 (66.67%) 9 | | |
| Headache subjects affected / exposed occurrences (all) | 9 / 12 (75.00%) 12 | | |
| Instability subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Insomnia | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 12 (33.33%) | | |
| occurrences (all) | 6 | | |
| Somnolence | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | | |
| occurrences (all) | 5 | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Temporomandibular pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Facial Dysesthesia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Olfactory nerve disorder | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Vlth nerve disorder | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Trigeminal nerve disorder | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |
| Hyperreflexia | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | | |
| Eye disorders Extraocular muscle paresis subjects affected / exposed occurrences (all) Nystagmus subjects affected / exposed occurrences (all) Diplopia subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1 | | |
| Gastrointestinal disorders Dysphagia subjects affected / exposed occurrences (all) Acid reflux (esophageal) subjects affected / exposed occurrences (all) Nausea with vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Isolated acute Abdominal pain | 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1 9 / 12 (75.00%) 12 5 / 12 (41.67%) 9 2 / 12 (16.67%) 3 | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 12 (8.33%)</p> <p>1</p> <p>1 / 12 (8.33%)</p> <p>2</p> <p>2 / 12 (16.67%)</p> <p>4</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Dry skin face</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin striae</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 12 (8.33%)</p> <p>1</p> <p>2 / 12 (16.67%)</p> <p>2</p> <p>1 / 12 (8.33%)</p> <p>1</p> | | |
| <p>Renal and urinary disorders</p> <p>Dysuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Polyuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 12 (8.33%)</p> <p>2</p> <p>1 / 12 (8.33%)</p> <p>1</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Muscle spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neck pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> | <p>1 / 12 (8.33%)</p> <p>1</p> <p>4 / 12 (33.33%)</p> <p>4</p> <p>1 / 12 (8.33%)</p> <p>1</p> | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Infections and infestations | | | |
| Bilateral otitis media | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Hyperphagia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 June 2017 | Changes in protocol and informed consent |
| 21 December 2017 | Protocol changes |
| 13 June 2018 | Importer/Manufacturing changes |
| 10 December 2018 | Protocol changes |
| 04 July 2019 | Protocol and Informed Consent changes due new team members and a principal investigator change |
| 03 June 2021 | Protocol changes |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported