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 ≤ -80°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 trás 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) Cushingoid facies subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3 3 / 12 (25.00%) 3		
Injury, poisoning and procedural complications Wound complication subjects affected / exposed occurrences (all) Incision site pain subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 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) Neurological decompensation subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Instability subjects affected / exposed occurrences (all) Insomnia	 1 / 12 (8.33%) 1 8 / 12 (66.67%) 9 9 / 12 (75.00%) 12 1 / 12 (8.33%) 1		

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

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

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