Clinical trial results:
A Phase 2/3, Multicenter, Multinational, Open-Label Study to Evaluate the Efficacy and Safety of ORGN001 (formerly ALXN1101) in Neonates, Infants, and Children with Molybdenum Cofactor Deficiency (MoCD) Type A

Summary

EudraCT number	2013-002702-30
Trial protocol	DE GB ES FR IT NO
Global end of trial date	13 September 2022

Results information

Result version number	v1 (current)
This version publication date	17 September 2023
First version publication date	17 September 2023

Trial information

Trial identification

Sponsor protocol code	ALXN1101-MCD-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02629393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Origin Biosciences (affiliate of BridgeBio)
Sponsor organisation address	Suite 250, 3160 Porter Drive, Palo Alto, CA, United States, 94304
Public contact	Business Development and Operations, Origin Biosciences (affiliate of BridgeBio), +1 650-391-9740 ,
Scientific contact	Business Development and Operations, Origin Biosciences (affiliate of BridgeBio), +1 650-391-9740 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001491-PIP01-13
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	11 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2022
Global end of trial reached?	Yes
Global end of trial date	13 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this clinical study was to evaluate the safety and efficacy of fosdenopterin in neonate, infant, and pediatric subjects with MoCD Type A who were either treatment-naïve or who had received compassionate use fosdenopterin.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

Background therapy: -

Evidence for comparator:

A placebo-controlled study was not feasible or ethical due to the severity of the untreated disease and reports of improved outcomes in patients with MoCD Type A who had been treated with rcPMP. Also, the lack of available treatment precluded inclusion of an active control arm.

Actual start date of recruitment	20 June 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Norway: 1
Worldwide total number of subjects	5
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	4
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	1
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Six subjects were screened for the study: 1 subject was a screen failure and 5 subjects were enrolled and received treatment. The subjects were recruited from Israel, Norway and United Kingdom.

Pre-assignment

Screening details:

Eligible neonates with a prenatal diagnosis of MoCD Type A were screened before or as soon as possible after birth. Eligible neonates who did not have a prenatal diagnosis of MoCD Type A but who had onset of signs and symptoms, underwent screening as soon as possible before receiving their first daily IV infusion of fosdenopterin.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Arm title	Subjects receiving fosdenopterin

Arm description:

Patients receiving daily intravenous (IV) infusions of fosdenopterin to neonates, infants, and children diagnosed with MoCD Type A who had not been previously treated with cyclic pyranopterin monophosphate (cPMP).

Arm type	Experimental
Investigational medicinal product name	Fosdenopterin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Infusion

Dosage and administration details:

Fosdenopterin (2.5 mg/vial and 12.5 mg/vial). Dose level: the Day 1 dose for term neonates (≥ 37 weeks GA), infants, and children was 700 µg/kg/day and for preterm neonates (< 37 weeks GA) was 525 µg/kg/day. Thereafter, the dose of fosdenopterin was to be incrementally escalated on Day 28 and at Months 3, 6, and 9 up to 1300 µg/kg/day (for patients enrolled before Protocol Amendment 3), or on Day 28 and at Month 3 up to 1200 µg/kg/day (for patients enrolled after Protocol Amendment 3) if the patient's clinical, PK, PD, and safety assessments permitted, including the absence of signs and symptoms of drug-related toxicity. Prior to dose escalation, each patient's data were reviewed by the Safety Review Committee (SRC) in conjunction with the Data Monitoring Committee (DMC). Dosing may have been escalated on or before Day 28, based on the Investigator and SRC/DMC review of all available data.

Number of subjects in period 1	Subjects receiving fosdenopterin
Started	5
Completed	2
Not completed	3
Physician decision	1

Failure to confirm MoCD Type A after genetic test	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
All subjects who have received at least one dose of Fosdenopterin.	

Reporting group values	Overall Study	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	4	4	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	1	1	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	3	3	
Male	2	2	

End points

End points reporting groups

Reporting group title	Subjects receiving fosdenopterin

Reporting group description:

Patients receiving daily intravenous (IV) infusions of fosdenopterin to neonates, infants, and children diagnosed with MoCD Type A who had not been previously treated with cyclic pyranopterin monophosphate (cPMP).

Primary: Overall survival

End point title	Overall survival[1]

End point description:

Patients with a confirmed diagnosis of MOCD Type A, treated with fosdenopterin and still alive at last observation.

End point type	Primary

End point timeframe:

Last observation

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: The analysis of OS was to be based on the Kaplan-Meier methodology for estimation of survival parameters. The analysis of OS was to be done using the FAS, the NmFAS, and the PmFAS. Two patients completed the study and 3 patients had discontinued before study completion. Due to the limited sample size, the analysis of OS was not performed.

End point values	Subjects receiving fosdenopterin			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Feeding pattern

End point title	Feeding pattern

End point description:

Patients with a confirmed diagnosis of MOCD Type A, treated with fosdenopterin and who can feed orally

End point type	Secondary

End point timeframe:

First 12 months

End point values	Subjects receiving fosdenopterin			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants				
Able to feed orally at Baseline	2			
Not able to feed orally at Baseline	1			
Able to feed orally at Last Observation	3			
Not able to feed orally at Last Observation	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 1 with ORGN001 treatment until study completion, up to Month 72.

Adverse event reporting additional description:

All-cause Mortality is zero in this study because there were no deaths that occurred. SAE Data presented is for all events occurring in >=1 patient.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Subjects receiving fosdenopterin

Reporting group description:

Patients receiving daily intravenous (IV) infusions of fosdenopterin to neonates, infants, and children diagnosed with MoCD Type A who had not been previously treated with cyclic pyranopterin monophosphate (cPMP).

Serious adverse events	Subjects receiving fosdenopterin		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Central venous catheterisation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Complication associated with device			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Catheter site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			

alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Viral tonsillitis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
alternative assessment type: Systematic				

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device leakage			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Subjects receiving fosdenopterin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)		
Surgical and medical procedures			
Central venous catheterisation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Complication associated with device			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	10		

Catheter site swelling alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2		
Catheter site rash alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Catheter site erythema alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Catheter site haemorrhage alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Respiratory, thoracic and mediastinal disorders Apnoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Rhinorrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2		
Product issues Device leakage alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Investigations			

Staphylococcus test positive alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Injury, poisoning and procedural complications Fall alternative assessment type: Systematic subjects affected / exposed occurrences (all) Contusion alternative assessment type: Systematic subjects affected / exposed occurrences (all) Skin laceration alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Congenital, familial and genetic disorders Ventricular septal defect alternative assessment type: Systematic subjects affected / exposed occurrences (all) Chiari network subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Cardiac disorders Cardiac failure alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2		
Nervous system disorders Seizure alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2		

Blood and lymphatic system disorders Anaemia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Eye disorders Conjunctival haemorrhage alternative assessment type: Systematic subjects affected / exposed occurrences (all) Eye discharge alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Gastrointestinal disorders Anal fissure alternative assessment type: Systematic subjects affected / exposed occurrences (all) Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Vomiting alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 2 / 5 (40.00%) 6		
Hepatobiliary disorders Hyperbilirubinaemia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Skin and subcutaneous tissue disorders Dermatitis alternative assessment type: Systematic			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Eczema			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Renal and urinary disorders			
Haematuria			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Infections and infestations			
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Pathogen resistance			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Catheter site infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Bacteraemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		
Viral tonsillitis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Otitis media acute				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Gastroenteritis viral				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Viral infection				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	3			
Tonsillitis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
COVID-19				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Bronchitis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Nasopharyngitis				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	4			
Oral herpes				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			

Conjunctivitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory syncytial virus infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Device related sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Device related infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypoglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Hypocalcaemia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2016	Amendment 1 (Protocol Version 2.0, 24 February 2016) was implemented to update the exploratory endpoints and study rationale.
23 November 2018	Amendment 1.1 (Protocol Version 2.1, 23 November 2018) was implemented to reflect new study sponsor, update study personnel, contact information and reporting requirements for Investigators when communicating SAEs and name of manufacturer.
15 February 2019	Amendment 2 (Protocol Version 3.0, 15 February 2019) was implemented to update the sponsor from Alexion Pharma GmbH to Origin Biosciences, rename ALXN1101 to fosdenopterin, extend the long-term treatment period from 48 to 60 months, update planned statistical analysis methods and sample size calculations based on the rarity of disease, update SAE reporting, add PD and PK sampling times, clarify that the Bayley-III tool could be used in children older than 42 months who had developmental delays, update blood sampling volumes, and update the criteria for study termination. Further, the primary efficacy endpoint was clarified to include that patient's with structural brain damage (e.g., hemiplegia or quadriplegia) or other pre-existing physical limitations not attributable to MoCD Type A would be excluded from the primary efficacy analysis.
14 November 2019	Amendment 3 (Protocol Version 4.0, 14 November 2019) was implemented to make additional text updates to reflect the prior addition of infants and children to the study population; adjust the study period to accommodate long-term follow-up; update the primary efficacy endpoint to be OS (and related text globally); add text and tables on the basis of a population PK model; update the primary objectives to include infants and pediatric patients who are either treatment naïve or who have received compassionate use of fosdenopterin; update the dosing and dose adjustment for term and preterm neonate patients to simplify the dosing strategy; update the secondary objectives to encompass evaluation of MoCD-associated urine and blood biomarker concentrations, the effect of fosdenopterin on growth and development, and the impact of fosdenopterin PK on PD biomarkers; and add and update secondary and exploratory efficacy endpoints text globally.
29 January 2020	Amendment 4 (Protocol Version 5.0, 29 January 2020) was implemented to update assessment and sampling time points and to update blood draw volumes.
10 September 2020	Amendment 4.1 (Protocol Version 5.1, 09 September 2020) was implemented as a regional amendment to add an exploratory study to include patients 6 to 17 years of age for EU member states.

Notes:

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.

Due to the small number of patients and no control, there was no SAP for this study. Results were reported by individual patient and were only descriptive.

Notes: