Clinical trial results:
A Phase 2/3 Open-Label, Single-Arm Trial to Evaluate the Safety and Activity of Eculizumab in Pediatric Patients with Relapsing Neuromyelitis Optica Spectrum Disorder

Summary

EudraCT number	2019-001829-26
Trial protocol	ES DE IT
Global end of trial date	31 July 2023

Results information

Result version number	v1 (current)
This version publication date	17 August 2024
First version publication date	17 August 2024

Trial information

Trial identification

Sponsor protocol code	ECU-NMO-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04155424
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000876-PIP03-14
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2023
Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the safety and efficacy of eculizumab in pediatric participants (aged 2 to < 18 years) with relapsing neuromyelitis optica spectrum disorder (NMOSD).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:
• Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
• Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
• Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	5
EEA total number of subjects	2

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)	2
Adolescents (12-17 years)	3

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All 5 participants were in the >=40 kilograms (kg) weight cohort at enrollment. Therefore, all 5 participants received the same dose of study drug for the Induction Period and the Maintenance Period as described in the study arm.

Period 1

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

Arms

Arm title	Eculizumab

Arm description:

Induction Period: Participants received eculizumab (900 milligrams [mg]) via intravenous (IV) infusion once a week for 4 weeks. Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks from fifth dose (Week 4) onwards and then every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	Soliris
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eculizumab was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Eculizumab
Started	5
Received at least 1 dose of study drug	5
Received study drug during Induction	5
Received study drug during Maintenance	5
Completed	0
Not completed	5
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Other than specified	3

Baseline characteristics

Reporting groups	
Reporting group title	Eculizumab
Reporting group description:	
Induction Period: Participants received eculizumab (900 milligrams [mg]) via intravenous (IV) infusion once a week for 4 weeks. Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks from fifth dose (Week 4) onwards and then every 2 weeks.	

Reporting group values	Eculizumab	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	12.0		
standard deviation	± 4.36	-	
Sex: Female, Male Units: participants			
Female	4	4	
Male	1	1	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	2	2	
More than one race	0	0	
Unknown or Not Reported	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	3	3	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Eculizumab

Reporting group description:

Induction Period: Participants received eculizumab (900 milligrams [mg]) via intravenous (IV) infusion once a week for 4 weeks. Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks from fifth dose (Week 4) onwards and then every 2 weeks.

Primary: Change between the Baseline Annualized Relapse Rate (ARR) and the On-Trial ARR at Week 52/53

End point title	Change between the Baseline Annualized Relapse Rate (ARR) and the On-Trial ARR at Week 52/53[1]

End point description:

ARR was calculated as the number of relapses for each participant divided by the number of years of treatment for that participant. Baseline ARR was based on 24 months prior to screening.

End point type	Primary

End point timeframe:

Baseline, Week 52/53

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 statistical analysis was not planned for this endpoint.

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: relapses/years on study				
arithmetic mean (standard deviation)	-3.01 (± 2.504)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to First On-trial Relapse

End point title	Time to First On-trial Relapse[2]

End point description:

Time to First Relapse was defined as beginning at the time the participant's first dose of eculizumab was administered until the participant’s first on-trial relapse was reported by the Investigator. Participants who did not experience an on-trial relapse were censored at the end of the study period. Full Analysis Set included all participants who received at least 1 dose of eculizumab. Note that since no participants experienced an On-trial Relapse, data was not collected for this Outcome Measure.

End point type	Primary

End point timeframe:

Baseline up to Week 52/53

Notes:

[2] - 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 statistical analysis was not planned for this endpoint.

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: weeks				
median (full range (min-max))	(to)			

Notes:

[3] - No participants experienced an On-trial Relapse.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Expanded Disability Status Scale (EDSS) Score at Week 52/53

End point title	Change from Baseline in Expanded Disability Status Scale (EDSS) Score at Week 52/53

End point description:

Disease-related disability was measured by the EDSS. The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments. A decrease in score indicates improvement. Full Analysis Set included all participants who received at least 1 dose of eculizumab. Here, overall number of participants analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 52/53

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: score on a scale				
arithmetic mean (standard deviation)	-0.75 (± 1.708)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shift from Baseline in Visual Acuity (VA)

End point title	Number of Participants With Shift from Baseline in Visual Acuity (VA)

End point description:

Snellen chart quantifies ability to read letters of varying sizes at a fixed distance in relation to the distance at which a participant with normal vision could read. Test was performed at a standard

distance, typically 6 meters or 20 feet. Snellen chart is typically recorded as acuity ratio distance (6 meters or 20 feet), so for normal VA it would be recorded as 20/20 or 6/6. Visual acuity was summarized according to the eye with greater worsening at end of primary treatment period. Data are presented for number of participants with a shift from baseline in VA presented per different levels of acuity ratio distance. Baseline: last available assessment prior to first IP study drug infusion regardless of treatment group. Visual Acuity data are only reported for the categories with available data at Baseline and Week 52/53. Full Analysis Set: all participants who received at least 1 dose of eculizumab. Overall number of participants analyzed= participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 52/53

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: participants				
Shift from VA 20/20-20/29 to VA 20/20-20/29	3			
Shift from VA 20/30-20/59 to VA 20/20-20/29	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) Score at Week 52/53

End point title	Change from Baseline in Pediatric Quality of Life Inventory (PedsQL) Score at Week 52/53

End point description:

PedsQL included a child self-report for participants 5 to 18 years with a 23-item PedsQL Generic Core Scales report. The PedsQL Generic Core Scales report included 4 scales, physical functioning, emotional functioning, social functioning, and school functioning. Each item used a 5-point rating scale (from 0=never to 4=almost always). Items are reverse scored and linearly transformed to a 0 (almost always) -100 (never) scale. All summary/total scores were mean of specific items where higher score indicated better HRQoL. Full Analysis Set included all participants who received at least 1 dose of eculizumab. Here, overall number of participants analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52/53

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: score on a scale				
arithmetic mean (standard deviation)	-5.01 (± 10.401)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Hauser Ambulation Index (HAI) Score at Week 52/53

End point title	Change from Baseline in the Hauser Ambulation Index (HAI) Score at Week 52/53

End point description:

The HAI evaluates gait and was used to assess the time and effort used by the participant to walk 25 feet (8 meters). The scale ranged from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst (restricted to wheel chair; unable to transfer self independently). A decrease in score indicates improvement. Full Analysis Set included all participants who received at least 1 dose of eculizumab. Here, overall number of participants analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Weeks 52/53

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: score on a scale				
arithmetic mean (standard deviation)	0.0 (± 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shift from Baseline in Confrontational Visual Fields (VF)

End point title	Number of Participants With Shift from Baseline in Confrontational Visual Fields (VF)

End point description:

Confrontational visual fields were summarized according to the number of quadrants with deficits across both eyes. Baseline was defined as the last available assessment prior to the first IP study drug infusion for all participants regardless of treatment group. Full Analysis Set included all participants who received at least 1 dose of eculizumab. Here, overall number of participants analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:
Baseline, Weeks 52/53

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: participants				
0 to 0	2			
2 to 0	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shift from Baseline in Color Vision

End point title	Number of Participants With Shift from Baseline in Color Vision

End point description:

Color vision was evaluated as the shift from baseline and described for participants with normal color vision at baseline in at least one eye. Participants with 13 or less correctly identified Ishihara plates were considered as having abnormal color vision, participants with 14 or more correctly identified plates were considered as having normal color vision. Baseline was defined as the last available assessment prior to the first IP study drug infusion for all participants regardless of treatment group. Full Analysis Set included all participants who received at least 1 dose of eculizumab. Here, overall number of participants analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:
Baseline, Weeks 52/53

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: participants				
No Change from Normal	4			
Worsened from Baseline	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Free Complement Protein 5 (C5) Concentrations at Week 52

End point title	Change From Baseline in Serum Free Complement Protein 5

	(C5) Concentrations at Week 52

End point description:

PK/PD analysis set included participants who received at least 1 dose of eculizumab and who had evaluable PK/PD data. for the endpoint. Here, overall number of participants analyzed signifies those participants who were evaluable for this outcome measure .

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: micrograms/milliliters				
arithmetic mean (standard deviation)				
Baseline	166.67 (± 50.203)			
Change from Baseline at Week 52	-166.64 (± 50.194)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Eculizumab Concentration at Week 52

End point title	Serum Eculizumab Concentration at Week 52

End point description:

Pharmacokinetic/Pharmacodynamic (PK/PD) analysis set included participants who received at least 1 dose of eculizumab and who had evaluable PK/PD data for the endpoint.

End point type	Secondary

End point timeframe:

Week 52

End point values	Eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: micrograms/milliliters				
arithmetic mean (standard deviation)				
Pre-dose: 5-90 Minutes	460.7 (± 65.04)			
Post-dose: 60 minutes	971.3 (± 198.04)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 53

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs) are AEs with a start date on or after the date of the first dose of study intervention. TEAEs were analyzed for Safety Set which included all participants who received at least 1 dose of eculizumab.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Eculizumab

Reporting group description:

Induction Period: Participants received eculizumab (900 mg) via IV infusion once a week for 4 weeks. Maintenance Period: Participants received eculizumab (1200 mg) via IV infusion every 2 weeks from fifth dose (Week 4) onwards and then every 2 weeks.

Serious adverse events	Eculizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Encephalitis meningococcal			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Eculizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
General disorders and administration site conditions			
Vaccination site pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Vaccination site erythema			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Feeling abnormal			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Amenorrhoea	Additional description: The N for this adverse event has been adjusted to the number of females in the study as it is a sex-specific event.		
subjects affected / exposed[1]	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Impulse-control disorder			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Investigations			
Weight increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Post vaccination fever			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Chalazion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Bowel movement irregularity			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		
Musculoskeletal and connective tissue disorders Kyphosis subjects affected / exposed occurrences (all) Growing pains subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 2 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1		
Infections and infestations Vulvovaginal candidiasis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Nasopharyngitis	 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Lactic acidosis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The N for this adverse event has been adjusted to the number of females in the study as it is a sex-specific event.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2019	It included following changes: - The study enrollment criteria on vaccination against meningococcal infections was updated to clarify that all participants must be vaccinated against meningococcal infections within the 3 years prior to, or at the time of, initiating study intervention. Participants who initiated study intervention treatment less than 2 weeks after receiving a meningococcal vaccine were to receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Participants were also to be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement-inhibitors (for example, eculizumab) instead of staying within the manufacturer's guidelines for vaccination times. - The study enrollment criterion on vaccination against Haemophilus influenzae and Streptococcus pneumoniae infections was updated to mention that this vaccination should be performed at least 2 weeks prior to dosing as per local and country-specific immunization guidelines for the appropriate age group.
03 May 2021	It included following changes: - The total sample size was decreased for the study based on updated sample size calculations. The number of participants enrolled was reduced from 15 to 12, and the number of evaluable participants for the primary analysis was reduced from 12 to 10. - Electrocardiograms (ECG) assessment was added to Week 26 for participants ≥ 20 kg, and added to Week 27 for participants 10 to < 20 kg. - Added text to clarify that vaccination was to be administered per local and country specific immunization guidelines for appropriate age groups. - Text was added to specify that supportive immunosuppressive therapies (ISTs) was to remain stable during the Screening Period. - Exclusion criterion was updated to clarify that a potential participant with active bacterial, viral, or fungal infection within 14 days prior to study intervention administration was to be excluded. - Exclusion criterion was added to exclude participants currently treated with a biologic medication that may affect immune system functioning.

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.

The study was terminated by Alexion, as only 5 of the planned 12 participants were enrolled due to difficulty in recruitment.

Notes: