Clinical trial results:
A Phase 3, Open-Label, Multicenter Study of ALXN1210 in Children and Adolescents With Atypical Hemolytic Uremic Syndrome (aHUS)

Summary

EudraCT number	2016-002499-29
Trial protocol	GB DE AT SE ES BE IT FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	16 July 2022
First version publication date	16 July 2022

Trial information

Trial identification

Sponsor protocol code	ALXN1210-aHUS-312

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03131219
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 787148158, clinicaltrials.eu@alexion.com
Scientific contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 787148158, 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-001943-PIP01-16
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	Interim
Date of interim/final analysis	06 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to assess the efficacy of ravulizumab to control disease activity in children and adolescents with aHUS who have not previously used a complement inhibitor (complement inhibitor treatment-naïve), as well as in complement inhibitor-experienced (eculizumab-experienced) adolescent participants.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2017
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	United States: 11
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	31
EEA total number of subjects	8

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)	4
Children (2-11 years)	17
Adolescents (12-17 years)	10

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:

This is an ongoing study and the data presented are the study results from the 26-week Initial Evaluation Period and data from the Extension Period through the data cutoff date at 03 Dec 2019.

Period 1

Period 1 title	Initial Evaluation Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Complement Inhibitor Treatment Naïve

Arm description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received ravulizumab at prespecified dose and timepoints.

Arm title	Eculizumab Experienced

Arm description:

Eculizumab-experienced participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received ravulizumab at prespecified dose and timepoints.

Number of subjects in period 1	Complement Inhibitor Treatment Naïve	Eculizumab Experienced
Started	21	10
Received At Least 1 Dose of Study Drug	21	10
Completed	17	10
Not completed	4	0
Adverse event, non-fatal	1	-
Deemed ineligible post treatment	2	-
Protocol deviation	1	-

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Complement Inhibitor Treatment Naïve

Arm description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Arm title	Eculizumab Experienced

Arm description:

Eculizumab-experienced participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Number of subjects in period 2	Complement Inhibitor Treatment Naïve	Eculizumab Experienced
Started	17	10
Received At Least 1 Dose of Study Drug	17	10
Completed	0	0
Not completed	17	10
Physician decision	1	-
Ongoing	16	10

Baseline characteristics

Reporting groups	
Reporting group title	Complement Inhibitor Treatment Naïve
Reporting group description:	
Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.	
Reporting group title	Eculizumab Experienced
Reporting group description:	
Eculizumab-experienced participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.	

Reporting group values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced	Total
Number of subjects	21	10	31
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	3	1	4
Children (2-11 years)	15	2	17
Adolescents (12-17 years)	3	7	10
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	6.7	11.0	
standard deviation	± 4.78	± 4.97	-
Sex: Female, Male Units: participants			
Female	11	1	12
Male	10	9	19
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	19	9	28
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	7	4	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	1	4

White	9	5	14
More than one race	1	0	1
Unknown or Not Reported	1	0	1
Weight at Time of First Infusion Units: Subjects			
≥5 to <10 kilograms	3	1	4
≥10 to <20 kilograms	9	1	10
≥20 to <30 kilograms	3	1	4
≥30 to <40 kilograms	3	1	4
≥40 to <60 kilograms	2	5	7
≥60 to <100 kilograms	1	1	2
Baseline Estimated Glomerular Filtration Rate (eGFR) Units: mL/min/1.73 m^2			
arithmetic mean	26.4	104.90	
standard deviation	± 21.17	± 29.545	-

End points

End points reporting groups

Reporting group title	Complement Inhibitor Treatment Naïve

Reporting group description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Reporting group title	Eculizumab Experienced

Reporting group description:

Eculizumab-experienced participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Reporting group title	Complement Inhibitor Treatment Naïve

Reporting group description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Reporting group title	Eculizumab Experienced

Reporting group description:

Eculizumab-experienced participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Primary: Percentage Of Complement Inhibitor Treatment-naïve Participants With Complete Thrombotic Microangiopathy (TMA) Response at Week 26

End point title	Percentage Of Complement Inhibitor Treatment-naïve Participants With Complete Thrombotic Microangiopathy (TMA) Response at Week 26[1][2]

End point description:

Complete TMA response during the 26-week Initial Evaluation Period is a composite endpoint that required normalization of hematological parameters (platelet count and lactate dehydrogenase) and improvement in kidney function (≥25% reduction in serum creatinine from baseline); for participants on dialysis, baseline was established at least 6 days after the end of dialysis. Participants had to meet these criteria for 2 separate assessments obtained at least 4 weeks apart, and any measurement in between. To be considered a responder, the latest time point a participant could first meet the response criteria was 28 days before the Week 26 (Day 183) assessment. Percentage based on the responders among treated participants. Full Analysis Set: all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, and met pre-specified eligibility criteria. Here, Overall 'Number of Participants Analyzed'= those who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Week 26

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: Only descriptive analysis was planned to be reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be reported for "Complement Inhibitor Treatment Naïve" arm only.

End point values	Complement Inhibitor Treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of participants				
number (confidence interval 95%)				
Complete TMA response	77.8 (52.4 to 93.6)			
Platelet count normalization	94.4 (72.7 to 99.9)			
LDH normalization	88.9 (65.3 to 98.6)			
≥25% improvement in serum creatinine from baseline	83.3 (58.6 to 96.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Complete TMA Response In Complement Inhibitor Treatment-naïve Participants

End point title	Time To Complete TMA Response In Complement Inhibitor Treatment-naïve Participants[3]

End point description:

Participants that did not have a response were censored at the date of last visit or study discontinuation at the time when the analysis was performed. The time to complete TMA Response is reported in days. The time of the event of a confirmed complete TMA response was considered the first time point at which all the criteria for complete TMA response were met. Participants had to meet all complete TMA response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Full Analysis Set (FAS): all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, and met pre-specified eligibility criteria. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through at least Week 52 and up to Week 111

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be reported for "Complement Inhibitor Treatment Naïve" arm only.

End point values	Complement Inhibitor Treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: days				
median (inter-quartile range (Q1-Q3))	30.0 (22.0 to 88.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Complement Inhibitor Treatment-naïve Participants With Complete TMA Response at Week 52

End point title	Proportion Of Complement Inhibitor Treatment-naïve Participants With Complete TMA Response at Week 52[4]

End point description:

The proportion of participants considered responders, along with a 2-sided 95% CI based on exact confidence limits using the Clopper Pearson method is reported. Full Analysis Set (FAS): all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, met pre-specified eligibility criteria, and had evaluable data at specified timepoint. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be reported for "Complement Inhibitor Treatment Naïve" arm only.

End point values	Complement Inhibitor Treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: proportion of participants				
number (confidence interval 95%)				
Complete TMA responder	0.882 (0.636 to 0.985)			
Platelet count normalization	0.882 (0.636 to 0.985)			
LDH normalization	1.000 (0.805 to 1.000)			
≥25% improvement in serum creatinine from baseline	1.000 (0.805 to 1.000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Do Not Require Dialysis at Weeks 26 and 52

End point title	Participants Who Do Not Require Dialysis at Weeks 26 and 52

End point description:

For participants requiring dialysis within 5 days prior to ALXN1210 treatment initiation, the number of participants no longer requiring dialysis is reported. Full Analysis Set (FAS): all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, met pre-specified eligibility criteria, and had evaluable data at specified timepoint. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this outcome measure and ‘Number Analyzed’ signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Week 26 and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	0[5]		
Units: participants				
Week 26	5			
Week 52	6			

Notes:

[5] - No participants were analyzed for this reporting group.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In eGFR At Weeks 26 and 52

End point title	Change From Baseline In eGFR At Weeks 26 and 52

End point description:

Kidney function evaluated by eGFR was summarized at baseline and the Week 26 and Week 52 time points using descriptive statistics for continuous variables for the observed value, as well as the change from baseline. The baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from Screening and the Day 1 visit). A value of 10 mL/min/1.73 m^2 for eGFR was imputed for participants requiring dialysis for acute kidney injury. The observed value and change from baseline are reported in mL/min/1.73 m^2. An increase indicated improvement in kidney function. Analysis population was Full Analysis Set. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this outcome measure and ‘Number Analyzed’ signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 26 and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	10		
Units: mL/min/1.73 m^2				
median (full range (min-max))				
Baseline (n=17, 10)	22.0 (10 to 84)	99.75 (54 to 136.5)		
Change From Baseline at Week 26 (n=17, 10)	80.0 (0 to 222)	-2.00 (-94 to 18)		
Change From Baseline at Week 52 (n=16, 10)	94.0 (10 to 230)	-3.00 (-20 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Change From Baseline In CKD Stage At Weeks 26 and 52

End point title	Participants With Change From Baseline In CKD Stage At Weeks 26 and 52

End point description:

The CKD stage (classified based on the National Kidney Foundation CKD Stage) is presented as the change from baseline in the participants that Improved (excluding those with Stage 1 [normal renal function] at baseline as they cannot improve), Worsened (excluding those with Stage 5 at baseline as they cannot worsen), and Stayed the Same, compared to the CKD stage at baseline. Baseline was derived based on the last available eGFR before starting treatment. Stage 5 was considered the worst category, while Stage 1 was considered the best category. A 2-sided 95% CI for the proportion, based on exact confidence limits using the Clopper-Pearson method, was provided for each category. Analysis population was Full Analysis Set. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint and ‘Number Analyzed’ signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 26, and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	10		
Units: participants				
Week 26, Improved (n=17, 10)	15	0		
Week 26, Worsened (n=17, 10)	0	3		
Week 26, Stayed the Same (n=17, 10)	2	7		
Week 52, Improved (n=16, 10)	16	0		
Week 52, Worsened (n=11, 10)	0	0		
Week 52, Stayed the Same (n=16, 10)	0	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Platelet Count At Weeks 26 and 52

End point title	Change From Baseline In Platelet Count At Weeks 26 and 52

End point description:

The hematologic TMA parameter of platelet count was summarized at baseline and at Week 26 and Week 52 using descriptive statistics for continuous variables for the change from baseline. Results are reported in platelets*10^9/liter (L) blood. Full Analysis Set (FAS): all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, met pre-specified eligibility criteria, and had evaluable data at the specified time point (Week 26 or Week 52). Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint and 'Number Analyzed' signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 26 and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	10		
Units: platelets*10^9/L				
median (full range (min-max))				
Baseline (n=18, 10)	51.25 (14 to 125)	281.75 (207 to 415.5)		
Change from Baseline at Week 26 (n=18, 10)	247.00 (57.5 to 368.5)	-2.25 (-74.5 to 123.5)		
Change from Baseline at Week 52 (n=17, 10)	213.00 (19.5 to 471.5)	-34.75 (-109 to 109)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In LDH At Weeks 26 and 52

End point title	Change From Baseline In LDH At Weeks 26 and 52

End point description:

The hematologic TMA parameter of serum LDH was summarized at baseline and at Week 26 and Week 52 using descriptive statistics for continuous variables for the change from baseline. Results are reported in units (U)/L serum. Full Analysis Set (FAS): all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, met pre-specified eligibility criteria, and had evaluable data at the specified timepoint (Week 26 or Week 52). Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint and 'Number Analyzed' signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 26 and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	10		
Units: U/L				
median (full range (min-max))				
Baseline (n=17, 10)	1963.00 (772 to 4985)	206.50 (138.5 to 356)		
Change From Baseline at Week 26 (n=16, 10)	-1851.50 (-4713 to -513)	-8.50 (-50.5 to 50.5)		
Change From Baseline at Week 52 (n=16, 10)	-1825.50 (-4724 to -579)	-17.50 (-34.5 to 29.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hemoglobin At Weeks 26 and 52

End point title	Change From Baseline In Hemoglobin At Weeks 26 and 52

End point description:

The hematologic TMA parameter of hemoglobin level was summarized at baseline and at Week 26 and Week 52 using descriptive statistics for continuous variables for the change from baseline. Results are reported in grams (g)/L blood. Full Analysis Set (FAS): all participants who received at least 1 dose of ravulizumab, had at least 1 post-baseline efficacy assessment, met pre-specified eligibility criteria, and had evaluable data at the specified timepoint (Week 26 or Week 52). Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint and 'Number Analyzed' signifies participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

Baseline, Week 26 and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	10		
Units: g/L				
median (full range (min-max))				
Baseline (n=18, 10)	74.25 (32 to 106)	132.00 (114.5 to 148)		
Change From Baseline at Week 26 (n=15, 10)	46.50 (26.5 to 86)	-3.50 (-19.5 to 8)		
Change From Baseline at Week 52 (n=17, 10)	51.50 (-19 to 80)	5.50 (-7.5 to 13.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Complement Inhibitor Treatment-naïve Participants With An Increase From Baseline In Hemoglobin ≥20 g/L Through Week 26 and Week 52

End point title	Percentage Of Complement Inhibitor Treatment-naïve Participants With An Increase From Baseline In Hemoglobin ≥20 g/L Through Week 26 and Week 52[6]

End point description:

The percentage of participants with an increase from baseline in hemoglobin ≥20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, was assessed through Week 26 and Week 52 and is presented as the percentage of responders, along with a 2-sided 95% CI. The 95% CIs are based on exact confidence limits using the Clopper-Pearson method. To be considered a responder during the 26-week and 52-week Extension Periods, the latest time point a participant could first meet the response criteria was 28 days before the respective Week 26 and Week 52 assessments (components of the response maintained for at least 28 days). Analysis population was Full Analysis Set. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through Week 26 and through Week 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be reported for "Complement Inhibitor Treatment Naïve" arm only.

End point values	Complement Inhibitor Treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage of participants				
number (confidence interval 95%)				
Week 26	100 (80.5 to 100)			
Week 52	94.1 (71.3 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Quality Of Life As Measured By The Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue Version 4 Questionnaire (Participants ≥5 Years Of Age) At Weeks 26 and 52

End point title	Change From Baseline In Quality Of Life As Measured By The Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue Version 4 Questionnaire (Participants ≥5 Years Of Age) At Weeks 26 and 52

End point description:

Quality of life was assessed in participants >5 years of age by the Pediatric FACIT-Fatigue Questionnaire (reported by participants who were ≥8 years of age at the time of enrollment; caregiver reported or caregiver assistance for participants who were 5 to <8 years of age at the time of enrollment). The FACIT Fatigue data were summarized at baseline and each post baseline time point using descriptive

statistics for continuous variables for the observed value as well as the change from baseline. The FACIT Fatigue Version 4 questionnaire at baseline and each post-infusion time point was scored using standard scoring algorithms. The score ranges from 0 to 52, with a higher score indicating less fatigue. An increase in score indicated an improvement in quality of life. Analysis population was Full Analysis Set. Here, Overall 'Number of Participants Analyzed' signifies those who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 26 and Week 52

End point values	Complement Inhibitor Treatment Naïve	Eculizumab Experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: units on a scale				
median (full range (min-max))				
Baseline	35.00 (4 to 44)	50.00 (42 to 52)		
Change From Baseline at Week 26	10.00 (4 to 48)	0.00 (-5 to 3)		
Change From Baseline at Week 52	9.00 (3 to 47)	-1.00 (-7 to 2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the beginning of the initial evaluation period (Day 1) through data cutoff (at least 52 weeks and up to a maximum of 111 weeks of treatment, representing 36.2 patient-years of exposure).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Complement Inhibitor Treatment Naïve

Reporting group description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Reporting group title	Eculizumab Experienced

Reporting group description:

Eculizumab-experienced participants received weight-based doses of ravulizumab during the 26-week Initial Evaluation Period. After the Initial Evaluation Period, participants rolled over into an Extension Period in which all participants continued their weight-based maintenance dose of ravulizumab.

Serious adverse events	Complement Inhibitor Treatment Naïve	Eculizumab Experienced	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 21 (66.67%)	1 / 10 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus enteritis			

subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human bocavirus infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Complement Inhibitor Treatment Naïve	Eculizumab Experienced	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	10 / 10 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 21 (28.57%)	1 / 10 (10.00%)	
occurrences (all)	7	1	
Hypotension			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Pyrexia			

subjects affected / exposed	10 / 21 (47.62%)	0 / 10 (0.00%)	
occurrences (all)	21	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 21 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Sinus disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	5 / 21 (23.81%)	1 / 10 (10.00%)	
occurrences (all)	6	1	
Rhinorrhoea			
subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	3 / 21 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Productive cough			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Product issues			
Device occlusion			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Investigations			

Influenza A virus test positive			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	3 / 21 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	
occurrences (all)	8	0	
Head injury			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Skin abrasion			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 21 (33.33%)	1 / 10 (10.00%)	
occurrences (all)	18	1	
Dizziness			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Anaemia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lacrimation increased			

subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 21 (23.81%)	1 / 10 (10.00%)	
occurrences (all)	9	1	
Diarrhoea			
subjects affected / exposed	6 / 21 (28.57%)	1 / 10 (10.00%)	
occurrences (all)	9	1	
Dyspepsia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lip dry			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	7 / 21 (33.33%)	1 / 10 (10.00%)	
occurrences (all)	24	1	
Constipation			
subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	
occurrences (all)	8	0	
Abdominal distension			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	
occurrences (all)	9	0	
Skin and subcutaneous tissue disorders			
Asteatosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Dermatitis diaper			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Osteochondrosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	
occurrences (all)	2	2	
Tenosynovitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 21 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 21 (14.29%)	4 / 10 (40.00%)	
occurrences (all)	4	16	
Nasopharyngitis			
subjects affected / exposed	7 / 21 (33.33%)	2 / 10 (20.00%)	
occurrences (all)	13	2	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)	2 / 10 (20.00%)	
occurrences (all)	4	2	
Otitis media			
subjects affected / exposed	0 / 21 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Pharyngitis			

subjects affected / exposed	2 / 21 (9.52%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Bronchitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	4	
Impetigo			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Viral infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Tonsilitis			
subjects affected / exposed	3 / 21 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Conjunctivitis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	3 / 21 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2018	•The loading dose for patients 5 to < 10 kg was increased from 300 milligrams (mg) to 600 mg. •The entry criteria were revised to allow enrollment into Cohort 2 of adolescent participants previously treated with eculizumab for at least the past 90 days. •Revised the entry criterion to allow LDH and hemoglobin results obtained during the Screening Period or within 28 days prior to the start of the Screening Period. •New objectives and endpoints were added to evaluate the safety and efficacy of ALXN1210 in Cohort 2. •Added 2 interim analyses: 1) when 12 to 14 complement inhibitor treatment-naïve participants (i.e., Cohort 1) have completed or withdrawn from the end of the 26-week Initial Evaluation Period; and 2) when all study participants have completed or withdrawn from the 26-week Initial Evaluation Period. •The Screening Period was clarified as 28 days for Cohort 2. •Added a provision to allow a supplemental dose of ALXN1210 to be administered to a participant if the Investigator and Sponsor mutually agree that a participant will potentially benefit. •Added a provision to allow for a dose to be administered as 2 separate infusions no more than approximately 24 hours apart if the Investigator and Sponsor mutually agree that the infusion volume (120 mL) of the loading dose for patients ≥ 5 to < 10 kg (600 mg) was too high for an individual participant. •The study sample size was increased to align with the planned sample size for each age category. • Statistical language was clarified to indicate that the analyses for Cohort 1 and Cohort 2 would be conducted and reported separately. •To reduce the participant data collection burden, removed the exploratory endpoints of Additional Signs or Symptoms of aHUS and Healthcare Resource Utilization.
16 July 2019	•Increased duration of the Extension Period from 2 years to 4.5 years or until the product is registered or approved (in accordance with country-specific regulations), whichever occurs first, to allow additional safety, pharmacokinetic/pharmacodynamic (PK/PD), and immunogenicity evaluations. •Revised schedule of assessments to align with the increased duration of the Extension Period. •To improve clarity, to differentiate early termination of participants from study versus discontinuation of ravulizumab treatment with continuation in the study (for monitoring visits) in the Extension Period. •Added criteria on TMA recurrence and guidance on retreatment with ravulizumab for participants who discontinue ravulizumab and remain in the study in the Extension Period. •Expanded secondary efficacy and PK/PD endpoints to include evaluation of participants who discontinue study drug as well as those who resume treatment. •The language in the Data Monitoring Committee was aligned with other protocols at a program level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported