



## Clinical trial results:

### Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult And Adolescent Patients With Atypical Hemolytic Uremic Syndrome (aHUS)

#### Summary

EudraCT number	2016-002027-29
Trial protocol	GB DE AT ES SE BE CZ IT
Global end of trial date	

#### Results information

Result version number	v1
This version publication date	22 July 2022
First version publication date	22 July 2022

#### Trial information

##### Trial identification

Sponsor protocol code	ALXN1210-aHUS-311
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02949128
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	12 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No
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Notes:

## General information about the trial

Main objective of the trial:

The purpose of the study is to assess the safety and efficacy of ravulizumab to control disease activity in adolescent and adult participants with aHUS who had not previously used a complement inhibitor.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2017
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	Australia: 4
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	58
EEA total number of subjects	27

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	49
From 65 to 84 years	9
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 of 02 Jul 2019.

### Period 1

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

### Arms

Arm title	Ravulizumab
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Arm description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Evaluation Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter. After the Initial Evaluation Period, participants entered an Extension Period and received ravulizumab until the product registration or approval (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
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	Ravulizumab
Started	58
Received At Least 1 Dose of Study Drug	58
Completed	49
Not completed	9
Adverse event, serious fatal	2
Physician decision	1
Adverse event, non-fatal	3
Failed to Meet Eligibility Criteria	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**

<b>Arm title</b>	Ravulizumab
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## Arm description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Evaluation Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter. After the Initial Evaluation Period, participants entered an Extension Period and received ravulizumab until the product registration or approval (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
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.

<b>Number of subjects in period 2</b>	Ravulizumab
Started	49
Received At Least 1 Dose of Study Drug	47
Completed	0
Not completed	49
Consent withdrawn by subject	5
Physician decision	2
Ongoing in Extension Period as of 07/02/2019	41
Protocol deviation	1

## Baseline characteristics

### Reporting groups

Reporting group title	Ravulizumab
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Reporting group description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Evaluation Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter. After the Initial Evaluation Period, participants entered an Extension Period and received ravulizumab until the product registration or approval (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

Reporting group values	Ravulizumab	Total	
Number of subjects	58	58	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	49	49	
From 65-84 years	9	9	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	43.4		
standard deviation	± 16.04	-	
Sex: Female, Male			
Units: participants			
Female	39	39	
Male	19	19	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	42	42	
Unknown or Not Reported	13	13	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	16	16	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	30	30	
More than one race	1	1	
Unknown or Not Reported	8	8	

## End points

### End points reporting groups

Reporting group title	Ravulizumab
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Reporting group description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Evaluation Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter. After the Initial Evaluation Period, participants entered an Extension Period and received ravulizumab until the product registration or approval (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

Reporting group title	Ravulizumab
-----------------------	-------------

Reporting group description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Evaluation Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter. After the Initial Evaluation Period, participants entered an Extension Period and received ravulizumab until the product registration or approval (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

### Primary: Percentage Of Participants With Complete Thrombotic Microangiopathy (TMA) Response at Week 26

End point title	Percentage Of Participants With Complete Thrombotic Microangiopathy (TMA) Response at Week 26 <sup>[1]</sup>
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End point description:

Complete TMA response during 26-week Initial Evaluation Period is a composite endpoint that required normalization of hematological parameters and improvement in kidney function ( $\geq 25\%$  reduction in serum creatinine from baseline); for participants on dialysis, baseline was established at least 6 days after end of dialysis. Participants had to meet these criteria for 2 separate assessments obtained at least 4 weeks apart, and any measurement in between. For a responder, latest time point a participant could first meet response criteria was 28 days before the Week 26 assessment. % was based on responders among treated participants. 95% CI: based on asymptotic Gaussian approximation method with a continuity correction. 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. Number of Participants Analyzed signifies participants evaluable for this endpoint.

End point type	Primary
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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 analyses was planned to be reported for this endpoint.

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of participants				
number (confidence interval 95%)				
Complete TMA Response	53.6 (39.6 to 67.5)			
Platelet count normalization	83.9 (73.4 to 94.4)			
LDH normalization	76.8 (64.8 to 88.7)			
$\geq 25\%$ improvement in serum creatinine from baseline	58.9 (45.2 to 72.7)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time To Complete TMA Response

End point title	Time To Complete TMA Response
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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. 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 (N) signifies those who were evaluable for this endpoint. 99999 signifies that the data were not available.

End point type	Secondary
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End point timeframe:

Baseline through Week 114

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: days				
median (inter-quartile range (Q1-Q3))	86.0 (42.0 to 99999)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion Of Participants With Complete TMA Response At Week 52

End point title	Proportion Of Participants With Complete TMA Response At Week 52
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End point description:

The proportion of participants considered responders, along with a 2-sided 95% CI for the Week 52 time point, is reported. To be considered a responder during the 26-week Initial Evaluation Period, the latest time point a participant could first meet the response criteria was 28 days before the Week 26 (Day 183) assessment (components of the response maintained for at least 28 days). 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 (Week 52).

End point type	Secondary
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End point timeframe:

Week 52



<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: proportion of participants				
number (confidence interval 95%)				
Complete TMA Response	0.500 (0.346 to 0.654)			
Platelet Count Normalization	0.909 (0.783 to 0.975)			
LDH Normalization	0.750 (0.597 to 0.868)			
≥25% improvement in serum creatinine from baseline	0.659 (0.501 to 0.795)			

### 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 (N) signifies those who were evaluable for this endpoint and Number Analyzed (n) signifies participants evaluable at specified time points.	
End point type	Secondary
End point timeframe:	
Week 26 and Week 52	

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Participants				
Week 26 (n=24)	16			
Week 52 (n=22)	16			

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline In Estimated Glomerular Filtration Rate (eGFR) At Weeks 26 and 52

End point title	Change From Baseline In Estimated Glomerular Filtration Rate (eGFR) At Weeks 26 and 52
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### End point description:

Kidney function evaluated by eGFR was summarized at baseline and Week 26 and Week 52 time points using descriptive statistics for continuous variables for the observed value, as well as change from baseline. Baseline value was defined as average of values from assessments performed prior to first study drug infusion (these could include results from Screening and Day 1 visit). A value of 10 mL/min/1.73 meters squared ( $m^2$ ) 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. 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, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.

End point type	Secondary
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### End point timeframe:

Baseline, Week 26 and Week 52

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: mL/min/1.73 $m^2$				
median (full range (min-max))				
Baseline (n=48)	10.00 (4 to 80)			
Change From Baseline at Week 26 (n=47)	29.00 (-13 to 108)			
Change From Baseline at Week 52 (n=43)	23.00 (-13 to 95)			

## 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
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### End point description:

The CKD stage is presented as change from baseline in 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 CKD stage at baseline. Baseline was derived based on the last available eGFR before starting treatment. Stage 5 was considered worst category, while Stage 1 was considered 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. 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, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.

End point type	Secondary
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### End point timeframe:

Baseline, Week 26, and Week 52

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants				
Week 26, Improved (n=47)	32			
Week 26, Worsened (n=47)	2			
Week 26, Stayed the Same (n=47)	13			
Week 52, Improved (n=43)	30			
Week 52, Worsened (n=12)	2			
Week 52, Stayed the Same (n=43)	11			

## 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 <sup>9</sup> /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 timepoints (Week 26 or 52). Here, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26 and Week 52	

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: platelets*10 <sup>9</sup> /L				
median (full range (min-max))				
Baseline (n=56)	95.25 (18 to 473)			
Change From Baseline at Week 26 (n=48)	125.00 (-126 to 338)			
Change From Baseline at Week 52 (n=44)	126.25 (-51.5 to 335)			

## 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. 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 timepoints (Week 26 or 52). Here, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.	
End point type	Secondary
End point timeframe: Baseline, Week 26 and Week 52	

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: U/L				
median (full range (min-max))				
Baseline (n=56)	508.00 (229.5 to 3249)			
Change From Baseline at Week 26 (n=48)	-310.75 (-3072 to 8.5)			
Change From Baseline at Week 52 (n=44)	-293.75 (-3107 to 81)			

### 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. 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 timepoints (Week 26 or 52). Here, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.	
End point type	Secondary
End point timeframe: Baseline, Week 26 and Week 52	

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: g/L				
median (full range (min-max))				
Baseline (n=56)	85.00 (60.5 to 140)			
Change From Baseline at Week 26 (n=56)	35.00 (-9 to 69)			
Change From Baseline at Week 52 (n=44)	41.75 (-25 to 83.5)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Of Complement Inhibitor Treatment-naïve Participants With An Increase From Baseline In Hemoglobin $\geq 20$ 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 $\geq 20$ g/L Through Week 26 and Week 52
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End point description:

The percentage of participants with an increase from baseline in hemoglobin  $\geq 20$  g/L, observed at 2 separate assessments obtained at least 4 weeks 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. 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). 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 timepoints (Week 26 or 52). Here, "N" signifies those who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline through Week 26 and through Week 52

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: percentage of participants				
number (confidence interval 95%)				
Week 26	75.5 (61.1 to 86.7)			
Week 52	86.4 (72.6 to 94.8)			

## Statistical analyses

**Secondary: Change From Baseline In Quality Of Life As Measured By The EuroQol 5-Dimension 3-Level (EQ-5D-3L) At Weeks 26 and 52**

End point title	Change From Baseline In Quality Of Life As Measured By The EuroQol 5-Dimension 3-Level (EQ-5D-3L) At Weeks 26 and 52
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## End point description:

The EQ-5D-3L is a participant-answered questionnaire that scores 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (scored as a 1, 2, or 3, with 3 being the worst health state), as well as health state on a visual analogue scale (0 to 100, with 100 representing the best health state). From these scores, a summary index score is derived using the time trade-off valuation set for the United States and ranges from -1 to 1, where a score above 0.94 indicates full health. An increase in score from baseline indicates improvement in quality of life. 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, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.

End point type	Secondary
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## End point timeframe:

Baseline, Week 26 and Week 52

End point values	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: units on a scale				
median (full range (min-max))				
Baseline (n=53)	0.59 (-0.113 to 0.753)			
Change from Baseline at Week 26 (n=46)	0.15 (-0.138 to 0.723)			
Change from Baseline at Week 52 (n=42)	0.26 (-0.143 to 0.707)			

**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 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 At Weeks 26 and 52
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## End point description:

Quality of life was evaluated in part using FACIT Fatigue Version 4. The data were summarized at baseline and at the Week 26 and Week 52 time point using descriptive statistics for continuous variables. The FACIT Fatigue Version 4 questionnaire at baseline and the Week 52 timepoint was scored using standard scoring algorithms. The score ranges from 0-52, with a higher score indicating less Fatigue. An increase in score indicated an improvement in quality of life. 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, "N" signifies those who were evaluable for this endpoint and "n" signifies participants evaluable for specified categories.

End point type	Secondary
End point timeframe:	
Baseline, Week 26 and Week 52	

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: units on a scale				
median (full range (min-max))				
Baseline (n=48)	24.00 (0 to 51)			
Change From Baseline at Week 26 (n=44)	20.00 (-16 to 48)			
Change From Baseline at Week 52 (n=40)	16.50 (-17 to 50)			

### 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 Week 114

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Ravulizumab
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Reporting group description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Evaluation Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter. After the Initial Evaluation Period, participants entered an Extension Period and received ravulizumab until the product registration or approval (in accordance with country-specific regulations) or for up to 4.5 years, whichever occurs first.

Serious adverse events	Ravulizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 58 (56.90%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Malignant hypertension			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula			



subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kidney transplant rejection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory disorder			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device leakage			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Biopsy kidney			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin increased			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Shunt occlusion			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lacunar infarction			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Atypical haemolytic uraemic syndrome			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toothache			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal haematoma			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal pseudoaneurysm			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
End stage renal disease			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Urinary tract infection			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia pyelonephritis			

subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fungaemia				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious colitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stenotrophomonas infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		



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

<b>Non-serious adverse events</b>	Ravulizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 58 (94.83%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 58 (22.41%)		
occurrences (all)	19		
Hypotension			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	13		
Fatigue			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	15		
Asthenia			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Face oedema			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Catheter site pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Immune system disorders			

Drug hypersensitivity subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 7		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Epistaxis subjects affected / exposed occurrences (all)	10 / 58 (17.24%) 15  10 / 58 (17.24%) 11  3 / 58 (5.17%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)  Insomnia subjects affected / exposed occurrences (all)  Depression subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 12  5 / 58 (8.62%) 5  3 / 58 (5.17%) 4		
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all)  Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5  5 / 58 (8.62%) 7		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 5		
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Dizziness subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 6		
Headache subjects affected / exposed occurrences (all)	22 / 58 (37.93%) 32		
Hypoaesthesia subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 58 (13.79%) 8		
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	19 / 58 (32.76%) 25		
Vomiting subjects affected / exposed occurrences (all)	18 / 58 (31.03%) 21		
Nausea subjects affected / exposed occurrences (all)	15 / 58 (25.86%) 21		

Constipation subjects affected / exposed occurrences (all)	9 / 58 (15.52%) 12		
Abdominal pain subjects affected / exposed occurrences (all)	7 / 58 (12.07%) 10		
Dyspepsia subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 58 (6.90%) 4		
Gastritis subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 6		
Rash subjects affected / exposed occurrences (all)	5 / 58 (8.62%) 5		
Dry Skin subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 6		
Pruritus subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Renal and urinary disorders			
End stage renal disease subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Haematuria subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	18		
Back pain			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	22		
Nasopharyngitis			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	22		
Oral herpes			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Device related infection			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Rhinitis			

subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	13		
Hypocalcaemia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Decreased appetite			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Vitamin D deficiency			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2016	Ravulizumab loading and maintenance doses were lowered for all body weight groups.
23 January 2017	<ul style="list-style-type: none"> <li>Added clarification to primary endpoint description that participants must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.</li> <li>Added clarification to secondary objectives (CKD stage as evaluated by eGFR; hemoglobin increase observed at 2 separate assessments obtained at least 4 weeks [28 days] apart, and any measurement in between).</li> <li>Revised Exclusion Criteria 2 to allow administration of the first dose of study drug while awaiting the results of stool Shiga toxin test results.</li> <li>Removed the requirement of systolic blood pressure <math>\leq 140</math> millimeters of mercury (mmHg) for at least 4 days.</li> <li>Added benefit/risk assessment text.</li> <li>Clarified withdrawal criteria to specify serious infusion reaction, severe uncontrolled infection, and pregnancy.</li> <li>Minor corrections and clarifications were made to the schedule of assessments and language describing drug packaging, storage, and preparation; prior/concomitant medications/procedures; prohibited medications; vaccination; contraception; medical history; vital signs; immunogenicity; suspected unexpected serious adverse reaction (SUSAR) reporting, adverse events; pharmacokinetic (PK)/pharmacodynamic (PD) assessment; genetics; statistical analysis; data monitoring committee (DMC); regulatory considerations; references; appendices.</li> </ul>
19 July 2017	<ul style="list-style-type: none"> <li>Revised Inclusion Criteria to include platelet count, LDH, and hemoglobin laboratory results during the Screening Period or within 28 days prior to the start of the Screening Period from a local laboratory; these changes allow participants with recent plasma exchange/plasma infusion (which alters laboratory results) to enter the study based on laboratory results prior to plasma exchange/plasma infusion.</li> <li>Continued to require that serum creatinine results for Inclusion Criterion must be based on central laboratory results from a specimen collected during the Screening Period. Since the primary endpoint is a change from baseline in creatinine, it is important to have both baseline and on-treatment serum samples from the same laboratory.</li> <li>Provided clarification that eligibility may be determined using results from tests carried out as standard of care for the treatment of the current TMA prior to a participant giving informed consent, including tests noted in Exclusion Criteria.</li> <li>Removed the requirement for culture/antigen test.</li> <li>Clarified participants with genetic defects in vitamin B12 metabolism (a rare cause of HUS not related to complement), rather than a deficit in vitamin B12, were excluded.</li> <li>Provided Sponsor opportunity to exclude participants on basis of risk to participant or impact on the interpretation of the efficacy or safety results for the study.</li> <li>Added a requirement to have at least 30 participants enrolled who met all 4 TMA requirements at Day 1 (platelet count of <math>&lt; 150,000/\text{microliter } (\mu\text{L})</math>, <math>\text{LDH} \geq 1.5 \times</math> upper limit of normal (ULN), hemoglobin <math>\leq</math> lower limit of normal (LLN), and serum creatinine level <math>\geq</math> ULN) to ensure that a majority of participants enrolled had abnormal baseline laboratory values.</li> <li>Provided the option for serum pregnancy tests to be used at any time points.</li> <li>Removed the option for "a designee" to perform the physical examination.</li> </ul>
19 July 2017	<ul style="list-style-type: none"> <li>Added pregnancy test assessment prior to first dose in Extension Period; removed requirement for pregnancy test to use urine (serum may now be used at all indicated timepoints).</li> <li>Clarified terminology on "meeting" vs "satisfying" inclusion and exclusion criteria and added option for the participant's legally authorized representative to provide informed consent.</li> <li>Corrected use of "assent" vs "consent".</li> <li>Clarified that there were separate tests for urine chemistry and urinalysis.</li> </ul>

07 May 2019	<ul style="list-style-type: none"> <li>• 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, PK/PD, and immunogenicity evaluations.</li> <li>• Revised schedule of assessments to align with the increased duration of the Extension Period.</li> <li>• Information on discontinuation of participants was clarified by differentiating early termination of participants from study versus discontinuation of ravulizumab treatment with continuation in the study for monitoring visit.</li> <li>• Added criteria on TMA recurrence and guidance on retreatment with ravulizumab for participants who discontinue ravulizumab and remain in the study.</li> </ul>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported