



Clinical trial results:

An Open-Label, Multi-Center Clinical Trial of Eculizumab in Pediatric Patients With Atypical Hemolytic-Uremic Syndrome

Summary

EudraCT number	2010-020310-28
Trial protocol	NL DE GB FR AT IT BE ES
Global end of trial date	08 January 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	C10-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01193348
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Incorporated
Sponsor organisation address	352 Knotter Drive, Cheshire , United States, 06410
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 1 47 10 06 06, clinicaltrials.eu@alxn.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +33 1 47 10 06 06, clinicaltrials.eu@alxn.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000876-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2014
Global end of trial reached?	Yes
Global end of trial date	08 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of eculizumab in pediatric patients with aHUS to control thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis and renal impairment.

Protection of trial subjects:

- vaccination against N. meningitidis, pneumococcus and haemophilus (per the vaccine label) at least 14 days prior to study drug initiation or otherwise be protected by prophylactic antibiotics.
- antibiotic prophylaxis throughout the treatment period for patients under age of two years.

Background therapy: -

Evidence for comparator:

No comparator was used in this trial.

Actual start date of recruitment	30 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	22
EEA total number of subjects	14

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)	5
Children (2-11 years)	13
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 27 patients diagnosed with aHUS signed the informed consent and of these, 22 patients were treated. Five patients were excluded from the study due to failed screening procedure and did not receive eculizumab.

Pre-assignment

Screening details:

At screening, patients had to have a platelet count < lower limit of normal range (<LLN) and serum creatinine level > 97 percentile for age; and had to exhibit signs or symptoms of hemolysis at the start of the current aHUS event with fragmented RBC and a negative Coombs test.

Pre-assignment period milestones

Number of subjects started	27 ^[1]
Number of subjects completed	22

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 5
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Informed consent form was obtained from parents/legal guardian for 27 pediatric patients. Of these 27 patients, 22 were treated in the study. The 5 other patients were considered as screen failure.

Period 1

Period 1 title	Treatment Period (26 Weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This trial was a single-arm study and blinding was not required.

Arms

Arm title	eculizumab
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Arm description:

Eculizumab: Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.

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

Dosage and administration details:

Eculizumab was to be administered intravenously (IV) according to the regimens described below. Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.

- If weight ≥ 40 kg: Induction: 900 mg weekly x 4; Maintenance: 1200 mg Wk5; 1200 mg Q2wks
- If weight 30 to <40 kg: Induction: 600 mg weekly x 2; Maintenance: 900 mg Wk3; 900 mg Q2wks
- If weight 20 to <30 kg: Induction: 600 mg weekly x 2; Maintenance: 600 mg Wk3; 600 mg Q2wks
- If weight 10 to <20 kg: Induction: 600 mg weekly x 1; Maintenance: 300 mg Wk2; 300 mg Q2wks
- If weight 5 to <10 kg: Induction: 300 mg Weekly x 1; Maintenance: 300 mg Wk2; 300 mg Q3wks

Number of subjects in period 1	eculizumab
Started	22
Completed	19
Not completed	3
Consent withdrawn by subject	1
Positive Shiga-Toxin Result vial Local	1
Serious Adverse Event	1

Period 2

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

Blinding implementation details:

This trial was a single-arm study and blinding was not required

Arms

Arm title	eculizumab
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Arm description:

Ecuzumab: Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.

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

Dosage and administration details:

Ecuzumab was to be administered intravenously (IV) according to the regimens described below. Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.

- If weight \geq 40 kg: Induction: 900 mg weekly x 4; Maintenance: 1200 mg Wk5; 1200 mg Q2wks
- If weight 30 to <40 kg: Induction: 600 mg weekly x 2; Maintenance: 900 mg Wk3; 900 mg Q2wks
- If weight 20 to <30 kg: Induction: 600 mg weekly x 2; Maintenance: 600 mg Wk3; 600 mg Q2wks
- If weight 10 to <20 kg: Induction: 600 mg weekly x 1; Maintenance: 300 mg Wk2; 300 mg Q2wks
- If weight 5 to <10 kg: Induction: 300 mg Weekly x 1; Maintenance: 300 mg Wk2; 300 mg Q3wks

Number of subjects in period 2 ^[2]	eculizumab
Started	17
Completed	16
Not completed	1
Physician decision	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients were allowed to continue participation in the study and to receive eculizumab in an Extension Treatment Period for 26 weeks or until the product is registered and available. Two patients did not continue in the Extension Treatment.

Period 3

Period 3 title	Post Treatment Period (discontinuation)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This trial was a single-arm study and blinding was not required

Arms

Arm title	eculizumab
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Arm description:

Patients who discontinued eculizumab treatment at any time during the study were followed for one year.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3 ^[3]	eculizumab
Started	10
Completed	8
Not completed	2
Lost to follow-up	2

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients who discontinued eculizumab treatment at any time were to be followed for one year. It concerned 10 patients: 3 discontinued before completing the 26-week Treatment Period, 2 did not continue in the Extension Treatment, 1 did not complete the Extension Phase, and 4 completed Extension Phase and were not transitioned to commercial eculizumab.

Baseline characteristics

Reporting groups

Reporting group title	eculizumab
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Reporting group description:

Ecuzumab: Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.

Reporting group values	eculizumab	Total	
Number of subjects	22	22	
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	5	5	
Children (2-11 years)	13	13	
Adolescents (12-17 years)	4	4	
Age continuous			
Units: years			
arithmetic mean	6.6		
standard deviation	± 6.06	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	12	12	
Platelet Category			
Units: Subjects			
< 150 x10 ⁹ /L	22	22	
≥ 150 x10 ⁹ /L	0	0	
LDH category			
Units: Subjects			
≤ ULN	3	3	
> ULN	19	19	
Number of patients with eGFR			
Units: Subjects			
<15 mL/min/1.73*m ²	10	10	
15-29 mL/min/1.73*m ²	4	4	
30-44 mL/min/1.73*m ²	2	2	
45-59 mL/min/1.73*m ²	2	2	
60-89 mL/min/1.73*m ²	2	2	
≥90 mL/min/1.73*m ²	2	2	
Chronic kidney disease (CKD)			
Units: Subjects			
Stage 0	0	0	
Stage 1	2	2	
Stage 2	2	2	
Stage 3a	2	2	
Stage 3b	2	2	
Stage 4	4	4	
Stage 5	10	10	

Plasma Therapy Duration			
Units: Subjects			
< 2 months	20	20	
>= 2 months	1	1	
Missing	1	1	
Clinical TMA Manifestation			
Units: Subjects			
First Clinical	16	16	
Multiple	5	5	
Missing	1	1	
Platelet Count			
Units: x10 ⁹ /L			
arithmetic mean	87.5		
standard deviation	± 42.34	-	
Lactate dehydrogenase			
Units: U/L			
arithmetic mean	1943.7		
standard deviation	± 1824.44	-	
Hemoglobin			
Units: g/L			
arithmetic mean	80.2		
standard deviation	± 15.3	-	
Creatinine			
Units: umol/L			
arithmetic mean	154.5		
standard deviation	± 116.43	-	

End points

End points reporting groups

Reporting group title	eculizumab
Reporting group description: Ecuzumab: Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.	
Reporting group title	eculizumab
Reporting group description: Ecuzumab: Fixed dosing is based on body weight cohorts. Adjustment of dose to accommodate patient growth is possible.	
Reporting group title	eculizumab
Reporting group description: Patients who discontinued eculizumab treatment at any time during the study were followed for one year.	

Primary: Proportion of Patients With Complete TMA Response

End point title	Proportion of Patients With Complete TMA Response ^[1]
End point description: Proportion of Patients with Complete TMA response was determined and defined by normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline which was sustained for at least two consecutive measurements obtained at least four weeks apart).	
End point type	Primary
End point timeframe: Through 26 weeks	

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: This study is a single arm trial and the system did not support statistical analyses for this single arm trial.

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	63.6 (40.7 to 82.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Complete Hematologic Response

End point title	Proportion of Patients With Complete Hematologic Response
End point description: Proportion of Patients with Complete Hematologic response through 26 weeks of treatment was determined and defined by normalization of platelet count and LDH sustained for at least two consecutive measurements obtained at least four weeks apart.	

End point type	Secondary
End point timeframe:	
Through 26 weeks	

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of participants				
number (confidence interval 95%)	81.8 (59.7 to 94.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Platelet Count Normalization

End point title	Proportion of Patients With Platelet Count Normalization
End point description:	
Proportion of Patients with Platelet Count Normalization through 26 weeks of treatment was determined and defined as the platelet count observed to be $\geq 150 \times 10^9/L$ on at least two consecutive measurements which span a period of at least four weeks.	
End point type	Secondary
End point timeframe:	
Through 26 weeks	

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of Participants				
number (confidence interval 95%)	95.5 (77.2 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Estimated Glomerular Filtration Rate (eGFR) Improvement

End point title	Proportion of Patients With Estimated Glomerular Filtration Rate (eGFR) Improvement
End point description:	
Proportion of Patients with Estimated Glomerular Filtration Rate (eGFR) Improvement was determined	

and defined as an increase in eGFR by ≥ 15 mL/min/1.73m² from baseline, sustained for at least two consecutive measurements obtained at least four weeks apart.

End point type	Secondary
End point timeframe:	
Through 26 weeks	

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of Participants				
number (confidence interval 95%)	86.4 (65.1 to 97.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet Count Change From Baseline to 26 Weeks

End point title	Platelet Count Change From Baseline to 26 Weeks
End point description:	
End point type	Secondary
End point timeframe:	
Through 26 weeks	

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: 10 ⁹ cells/L				
least squares mean (confidence interval 95%)	204.96 (164.44 to 245.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Complete TMA Response

End point title	Proportion of Patients With Complete TMA Response
End point description:	
Proportion of Patients with Complete TMA response was determined and defined by normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from	

baseline which was sustained for at least two consecutive measurements obtained at least four weeks apart).

End point type	Secondary
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End point timeframe:

Through End of Study, Median Exposure 55 Weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of Participants				
number (confidence interval 95%)	68.2 (45.1 to 86.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Complete Hematologic Response

End point title	Proportion of Patients With Complete Hematologic Response
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End point description:

Proportion of Patients with Complete Hematologic response through end of study was determined and defined by normalization of platelet count and LDH sustained for at least two consecutive measurements obtained at least four weeks apart.

End point type	Secondary
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End point timeframe:

Through End of Study, Median Exposure 55 Weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of Participants				
number (confidence interval 95%)	90.9 (70.8 to 98.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Platelet Count Normalization

End point title	Proportion of Patients With Platelet Count Normalization
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End point description:

Proportion of Patients with Platelet Count Normalization through end of study was determined and

defined as the platelet count observed to be $\geq 150 \times 10^9/L$ on at least two consecutive measurements which span a period of at least four weeks

End point type	Secondary
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End point timeframe:

Through End of Study, Median Exposure 55 Weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of Participants				
number (confidence interval 95%)	95.5 (77.2 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients With Estimated Glomerular Filtration Rate (eGFR) Improvement

End point title	Proportion of Patients With Estimated Glomerular Filtration Rate (eGFR) Improvement
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End point description:

Proportion of Patients with Estimated Glomerular Filtration Rate (eGFR) Improvement was determined and defined as an increase in eGFR by ≥ 15 mL/min/1.73m² from baseline, sustained for at least two consecutive measurements obtained at least four weeks apart.

End point type	Secondary
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End point timeframe:

Through End of Study, Median Exposure 55 Weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Percentage of Participants				
number (confidence interval 95%)	86.4 (65.1 to 97.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet Count Change From Baseline to 52 Weeks

End point title	Platelet Count Change From Baseline to 52 Weeks
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End point description:

End point type	Secondary
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End point timeframe:

Through 52 Weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: 10 ⁹ cells/L				
least squares mean (confidence interval 95%)	165.43 (98.43 to 232.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 5 to <10kg) N=3

End point title	Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 5 to <10kg) N=3
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End point description:

Pharmacokinetic (PK) parameters C_{min} and C_{max} were estimated using a population PK model developed from the observed PK concentration data.

End point type	Secondary
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End point timeframe:

Induction Phase was between 1 and 4 weeks in length depending on patient weight cohort. Maintenance Phase was started 1 week after induction phase and dosing of eculizumab administration was every 2 weeks or every 3 weeks depending on patient weight cohort

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)				
Min Concentration during induction period	223.2 (± 19)			
Max concentration during induction period	312.8 (± 51.2)			
Min concentration during maintenance	187.2 (± 42)			
Max concentration during maintenance	499.7 (± 27.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 10 to <20kg) N=7

End point title	Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 10 to <20kg) N=7
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End point description:

Pharmacokinetic (PK) parameters C_{min} and C_{max} were estimated using a population PK model developed from the observed PK concentration data.

End point type	Secondary
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End point timeframe:

Induction Phase was between 1 and 4 weeks in length depending on patient weight cohort. Maintenance Phase was started 1 week after induction phase and dosing of eculizumab administration was every 2 weeks or every 3 weeks depending on patient weight cohort

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)				
Min Concentration during induction period	297.2 (± 74.7)			
Max concentration during induction period	436.2 (± 128.3)			
Min concentration during maintenance	241.8 (± 106)			
Max concentration during maintenance	459.5 (± 105.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 20 to <30kg) N=6

End point title	Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 20 to <30kg) N=6
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End point description:

Pharmacokinetic (PK) parameters C_{min} and C_{max} were estimated using a population PK model developed from the observed PK concentration data.

End point type	Secondary
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End point timeframe:

Induction Phase was between 1 and 4 weeks in length depending on patient weight cohort. Maintenance Phase was started either 2 weeks or 3 weeks after induction phase depending on patient weight cohort.

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)				
Min Concentration during induction period	185.1 (± 19.5)			
Max concentration during induction period	242.5 (± 24.5)			
Min concentration during maintenance	337.6 (± 43.4)			
Max concentration during maintenance	579.5 (± 66.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 30 to <40kg) N=1

End point title	Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort 30 to <40kg) N=1
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End point description:

Pharmacokinetic (PK) parameters C_{min} and C_{max} were estimated using a population PK model developed from the observed PK concentration data.

Of note, no subjects were in the maintenance phase because the patient in the 30 to <40 kg cohort group was changed to the ≤ 40 kg body weight cohort category.

Ecuzumab Minimum and Maximum Blood Concentration during Maintenance is not mentioned because Non Applicable because N=6 in the Maintenance Phase because the patient in the 30 - <40kg cohort group changed to the ≥40kg body weight category.

End point type	Secondary
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End point timeframe:

Induction Phase was between 1 and 4 weeks in length depending on patient weight cohort. Maintenance Phase was started either 2 weeks or 3 weeks after induction phase depending on patient weight cohort

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: microgram(s)/millilitre				
number (not applicable)				
Min Concentration during induction period	196.8			
Max concentration during induction period	282.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort ≥ 40 kg) N=5

End point title	Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration (Body Weight Cohort ≥ 40 kg) N=5
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End point description:

Pharmacokinetic (PK) parameters C_{min} and C_{max} were estimated using a population PK model developed from the observed PK concentration data.

Of note, 6 subjects were considered for the maintenance phase, because the patient in the 30 to <40 kg body weight cohort group was changed to the ≥ 40 kg body weight category.

End point type	Secondary
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End point timeframe:

Induction Phase was between 1 and 4 weeks in length depending on patient weight cohort. Maintenance Phase was started either 2 weeks or 3 weeks after induction phase depending on patient weight cohort

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: microgram(s)/millilitre				
arithmetic mean (standard deviation)				
Min Concentration during induction period	125.5 (\pm 26.3)			
Max concentration during induction period	180.9 (\pm 42.6)			
Min concentration during maintenance	278.4 (\pm 130.3)			
Max concentration during maintenance	572.4 (\pm 267.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through end of study; exposure to eculizumab in this study extended for a median duration of 12.6 months and ranged from 1 dose to 24.5 months.

Adverse event reporting additional description:

At every visit, patients were asked a standard non-leading question to elicit any changes in their medical well-being including inquiry about any hospitalization, accidents and new or changed concomitant medication regimens. AEs were also documented from any data collected (e.g. laboratory values, physical examination findings, ECG changes, etc.)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	eculizumab
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Reporting group description:

Information on TEAEs was collected during the study (occurrence from the time of first eculizumab infusion and after) and during the Follow-up Period (12 weeks after the last dose of eculizumab).

Serious adverse events	eculizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 22 (59.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device malfunction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical device complication			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillar haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related sepsis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis viral			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			

subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	eculizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 22 (90.91%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Pallor			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Surgical and medical procedures Central venous catheter removal subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Application site eczema subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Chest pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Drug withdrawal syndrome subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Fatigue subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Injection site rash subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Injection site haematoma subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Malaise subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Oedema peripheral			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 22 (4.55%)</p> <p>1</p> <p>11 / 22 (50.00%)</p> <p>12</p>		
<p>Immune system disorders</p> <p>Drug hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 22 (4.55%)</p> <p>1</p>		
<p>Reproductive system and breast disorders</p> <p>Vaginal haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 22 (4.55%)</p> <p>1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>OROPHARYNGEAL PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleural effusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rhinorrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tonsillar hypertrophy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 22 (40.91%)</p> <p>9</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>3 / 22 (13.64%)</p> <p>3</p> <p>2 / 22 (9.09%)</p> <p>2</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p>		
<p>Psychiatric disorders</p>			

Food aversion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Mood altered subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Investigations			
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Electrocardiogram T wave inversion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Electroencephalogram abnormal subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Weight increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Injury, poisoning and procedural complications			
Animal bite subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Contusion subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Infusion related reaction subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Joint dislocation subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Scratch			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Nail injury subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Procedural pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Nervous system disorders Demyelinating polyneuropathy subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Headache subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 5		
Sinus headache subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 3		
Leukopenia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Neutropenia			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphadenopathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 22 (4.55%)</p> <p>1</p> <p>2 / 22 (9.09%)</p> <p>2</p> <p>1 / 22 (4.55%)</p> <p>1</p>		
<p>Ear and labyrinth disorders</p> <p>Ear pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 22 (4.55%)</p> <p>1</p>		
<p>Eye disorders</p> <p>Eye discharge</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ulcerative keratitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vision blurred</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p> <p>1 / 22 (4.55%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>ABDOMINAL DISCOMFORT</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p>	<p>1 / 22 (4.55%)</p> <p>1</p> <p>7 / 22 (31.82%)</p> <p>8</p> <p>2 / 22 (9.09%)</p> <p>2</p> <p>2 / 22 (9.09%)</p> <p>2</p>		

subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	8		
Abdominal distension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	7		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dermatitis diaper			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Increased tendency to bruise			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pruritus			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Purpura			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Rash erythematous			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Glycosuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Microalbuminuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Polyuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Beta haemolytic streptococcal infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Candiduria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

Catheter site infection			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Conjunctivitis viral			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Genital candidiasis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	7		
Oral fungal infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		

Pathogen resistance			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pyelonephritis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Varicella			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Metabolic disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2010	Modification of protocol inclusion criteria, in particular to include patients with atypical hemolytic-uremic syndrome (aHUS) from 1 month of age and body weight \geq 5kg
07 November 2011	Modification to the clinical study protocol to increase the number of patients to be enrolled in the clinical study, to update change in personnel and recruitment period, and to include country-specific requirements in a global version of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/21877169>