Clinical trial results:
EVALUATING THE MORPHOFUNCTIONAL EFFECTS OF ECULIZUMAB THERAPY IN PRIMARY MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS: A PILOT, SINGLE ARM STUDY IN TEN PATIENTS WITH PERSISTENT HEAVY PROTEINURIA

Summary

EudraCT number	2013-003826-10
Trial protocol	IT
Global end of trial date	24 May 2017

Results information

Result version number	v1 (current)
This version publication date	08 June 2019
First version publication date	08 June 2019
Summary attachment (see zip file)	Paper (Ruggenenti_C5 convertase blockade in MPGN.pdf) Paper (Supplementary_1.pdf)

Trial information

Trial identification

Sponsor protocol code	EAGLE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02093533
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	V. G. B. Camozzi, 3, Ranica / Bergamo, Italy, 24020
Public contact	Piero Ruggenenti, Centro di Ricerche Cliniche Aldo e Cele Daccò V. G. B. Camozzi, 3 Ranica (BG), 0039 0354535301, piero.ruggenenti@marionegri.it
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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	Final
Date of interim/final analysis	06 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2017
Global end of trial reached?	Yes
Global end of trial date	24 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether Eculizumab therapy may reduce 24 hour proteinuria, considered as a continuous variable, at 6 months (week-24) and 12 months (week-48) compared to baseline.

Protection of trial subjects:

The Agenzia Italiana del Farmaco and ethics committees of participating centers approved the study. It was conducted in conformance with Declaration of Helsinki, Good Clinical Practice standards and applicable country regulations regarding ethical committee review, informed consent, protection of human subjects participating in biomedical research and privacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	5

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 04/03/2014, to 07/01/2015, 10 patients were included from 6 Centres. Eligible patients were those in a prospective cohort who had been referred to the Italian Registry of membranoproliferative glomerulonephritis at the Aldo e Cele Daccò Clinical Research Center for Rare Disease of the istituto di Ricerche farmacologiche Mario Negri IRCCS

Pre-assignment

Screening details:

205 patients with biopsy-proven MPGN referred to the Italian MPGN Registry at April 2014. 14 excluded for secondary MPGN, 17 started dialysis, 33 underwent a kidney transplant, 40 had a normal C3, 92 with proteinuria<3.5 g/24h and/or sC5b9 <1000.
9 and 1 spontaneously referred patients fulfilled all the selection criteria and they was enrolled

Period 1

Period 1 title	Eculizumab first 1-year
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eculizumab first 1-year

Arm description:

After Baseline visit, consenting patients were transferred to the patients were transferred to the Unit of Nephrology of the Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII of Bergamo, where they received the first intravenous infusion of eculizumab (Soliris; Alexion Pharmaceuticals) under the supervision of an intensivist. Adults and underage patients who weighed ≥40 kg received 900 mg of eculizumab every week for 4 weeks (induction period), 1,200 mg at week 5, and then 1,200 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment. The children who weighed < 40 kg received 600 mg of eculizumab every week for 2 weeks (induction period), 900 mg at week 3, and then 900 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment.

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

Dosage and administration details:

Patients received the first intravenous infusion of eculizumab under the supervision of an intensivist. Adults and underage patients who weighed ≥40 kg received 900 mg of eculizumab every week for 4 weeks (induction period), 1,200 mg at week 5, and then 1,200 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment.
Patients weighed < 40 kg received 600 mg of eculizumab every week for 2 weeks (induction period), 900 mg at week 3, and then 900 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment is .
A second identical 48-week treatment course was started after the 12-week eculizumab withdrawal (washout period).

Number of subjects in period 1	Eculizumab first 1-year
Started	10
Completed	10

Period 2

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

Arms

Arm title	Eculizumab washout period

Arm description:

After completion of the EAGLE study- first 1-year, key laboratory and safety parameters will be evaluated at 1,2 and 3 months after Eculizumab withdrawal. GFR, albumin, IgG and sodium fractional clearance will be evaluated only at the end of the month 3. The investigators, however, will have the possibility to anticipate Eculizumab administration before completion of the 3-month period in case of events conceivably related to Eculizumab withdrawal that might harm the study patient.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Eculizumab washout period
Started	10
Completed	10

Period 3

Period 3 title	Eculizumab second 1-year
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Eculizumab second 1-year

Arm description:

After the washout period or before completion of the 3-month period due to investigator's decision (in case of events conceivably related to Eculizumab withdrawal that might harm the study patient) patients will receive the first intravenous infusion of Eculizumab and will enter a second 1-year Eculizumab treatment period.
During the second 1-year Treatment Period, patients will be treated exactly as described for the previous year of treatment. During the whole Extension Treatment Period key laboratory and safety parameters will be evaluated whenever deemed clinically appropriate, in particular for safety reasons.

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

Dosage and administration details:

Patients received the first intravenous infusion of eculizumab under the supervision of an intensivist.
Adults and underage patients who weighed ≥40 kg received 900 mg of eculizumab every week for 4 weeks (induction period), 1,200 mg at week 5, and then 1,200 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment.
Patients weighed < 40 kg received 600 mg of eculizumab every week for 2 weeks (induction period), 900 mg at week 3, and then 900 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment is .
A second identical 48-week treatment course was started after the 12-week eculizumab withdrawal (washout period).

Number of subjects in period 3	Eculizumab second 1-year
Started	10
Completed	9
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Eculizumab first 1-year

Reporting group description: -

Reporting group values	Eculizumab first 1-year	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	5	5	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	20		
standard deviation	± 6.9	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	6	6	
Nefs Units: Subjects			
Detectable	5	5	
Non Detectable	5	5	
Weight Units: kilogram(s)			
arithmetic mean	59.1		
standard deviation	± 15	-	
BMI Units: Kg/m2			
arithmetic mean	21.5		
standard deviation	± 3.3	-	
Systolic BP Units: mm Hg			
arithmetic mean	120.8		
standard deviation	± 14	-	
Diastolic BP Units: mm Hg			
arithmetic mean	74.8		
standard deviation	± 13	-	
Pulse rate Units: beats/min			
arithmetic mean	71.4		
standard deviation	± 10.7	-	
sC5b-9 Units: ng/mL			

median	2.420		
inter-quartile range (Q1-Q3)	1.915 to 3.330	-	
C3			
Units: mg/dL			
median	14.5		
inter-quartile range (Q1-Q3)	10.3 to 24.4	-	
Serum Creatinine			
Units: mg/dL			
arithmetic mean	1.21		
standard deviation	± 1	-	
Serum Albumin			
Units: g/dL			
arithmetic mean	2.4		
standard deviation	± 0.5	-	
Serum Protein			
Units: g/dL			
arithmetic mean	4.6		
standard deviation	± 0.8	-	
Total cholesterol			
Units: mg/dL			
arithmetic mean	228.4		
standard deviation	± 30	-	
HDL cholesterol			
Units: mg/dL			
arithmetic mean	47.5		
standard deviation	± 13	-	
LDL cholesterol			
Units: mg/dL			
arithmetic mean	148.6		
standard deviation	± 39	-	
Triglycerides			
Units: mg/dL			
median	103		
inter-quartile range (Q1-Q3)	77 to 231	-	
Blood Glucose			
Units: mg/dL			
arithmetic mean	88.3		
standard deviation	± 10	-	
Hemoglobin			
Units: g/dL			
arithmetic mean	11.3		
standard deviation	± 1.7	-	
Serum calcium			
Units: mg/dL			
arithmetic mean	8.3		
standard deviation	± 0.4	-	
Serum phosphate			
Units: mg/dL			
arithmetic mean	5.5		
standard deviation	± 0.7	-	
Serum potassium			
Units: mEq/L			

arithmetic mean	4.7		
standard deviation	± 0.7	-	
mGFR			
Units: mL/min/1.73m2			
arithmetic mean	69.7		
standard deviation	± 35.2	-	
eGFR			
Units: mL/min/1.73m2			
arithmetic mean	136.8		
standard deviation	± 94.8	-	
Urinary protein			
Units: g/24h			
median	6.03		
inter-quartile range (Q1-Q3)	4.8 to 12.4	-	
Urinary albumin			
Units: µg/min			
median	3.199		
inter-quartile range (Q1-Q3)	2.302 to 5.660	-	
Urinary sodium			
Units: mEq/24h			
median	107.4		
inter-quartile range (Q1-Q3)	93 to 171	-	
Albumin fractional clearance			
Units: Adimensional			
median	237.7		
inter-quartile range (Q1-Q3)	117 to 580	-	
IgG fractional clearance			
Units: Adimensional			
median	42.3		
inter-quartile range (Q1-Q3)	22.6 to 195.8	-	

End points

End points reporting groups

Reporting group title	Eculizumab first 1-year

Reporting group description:

After Baseline visit, consenting patients were transferred to the patients were transferred to the Unit of Nephrology of the Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII of Bergamo, where they received the first intravenous infusion of eculizumab (Soliris; Alexion Pharmaceuticals) under the supervision of an intensivist. Adults and underage patients who weighed ≥40 kg received 900 mg of eculizumab every week for 4 weeks (induction period), 1,200 mg at week 5, and then 1,200 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment. The children who weighed < 40 kg received 600 mg of eculizumab every week for 2 weeks (induction period), 900 mg at week 3, and then 900 mg every 14 ± 2 days (maintenance period), up to completion of 48 weeks of treatment.

Reporting group title	Eculizumab washout period

Reporting group description:

After completion of the EAGLE study- first 1-year, key laboratory and safety parameters will be evaluated at 1,2 and 3 months after Eculizumab withdrawal. GFR, albumin, IgG and sodium fractional clearance will be evaluated only at the end of the month 3. The investigators, however, will have the possibility to anticipate Eculizumab administration before completion of the 3-month period in case of events conceivably related to Eculizumab withdrawal that might harm the study patient.

Reporting group title	Eculizumab second 1-year

Reporting group description:

After the washout period or before completion of the 3-month period due to investigator's decision (in case of events conceivably related to Eculizumab withdrawal that might harm the study patient) patients will receive the first intravenous infusion of Eculizumab and will enter a second 1-year Eculizumab treatment period.
During the second 1-year Treatment Period, patients will be treated exactly as described for the previous year of treatment. During the whole Extension Treatment Period key laboratory and safety parameters will be evaluated whenever deemed clinically appropriate, in particular for safety reasons.

Primary: Change in 24-hour proteinuria at 24 and 48 weeks after eculizumab first 1-year

End point title	Change in 24-hour proteinuria at 24 and 48 weeks after eculizumab first 1-year[1]

End point description:

End point type	Primary

End point timeframe:

The primary efficacy outcome was 24-hour proteinuria at 24 and 48 weeks of the first treatment period as compared to baseline.

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: During first year treatment are reported p values at week 24 (p=0.01) and week 48 (p=0.006) vs baseline.
Signed rank test performed.

End point values	Eculizumab first 1-year			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: g/24h				
median (inter-quartile range (Q1-Q3))				
Urinary Protein excreation 24 week	3.74 (3.2 to 4.4)			

Urinary Protein excreation 48 week	5.06 (3.1 to 5.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in 24-hour proteinuria after the washout period

End point title	Change in 24-hour proteinuria after the washout period[2]

End point description:

Proteinuria after the washout period compared to the end of the first 1-year Eculizumab treatment

End point type	Primary

End point timeframe:

Proteinuria after the washout period

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: After wash out is reported p values (p=0.8) vs baseline.
Signed rank test performed.

End point values	Eculizumab washout period			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Urinary Protein Excretion				
median (inter-quartile range (Q1-Q3))				
urinary protein excretion	7.02 (4.3 to 9.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in 24-hour proteinuria at 24 and 48 weeks after Eculizumab second 1-year

End point title	Change in 24-hour proteinuria at 24 and 48 weeks after Eculizumab second 1-year[3]

End point description:

End point type	Primary

End point timeframe:

The primary efficacy outcome was 24-hour proteinuria at 24 and 48 weeks of the second treatment period as compared to baseline.

Notes:

[3] - 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: During second year treatment are reported p values at week 24 (p=0.4) and week 48 (p=0.5) vs baseline.
Signed rank test performed.

End point values	Eculizumab second 1-year			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: g/24h				
median (inter-quartile range (Q1-Q3))				
Urinary Protein Excreation 24 week	6.06 (3.4 to 8.1)			
Urinary Protein Excreation 48 week	7.79 (2.1 to 8.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete or partial remission of the nephrotic syndrome

End point title	Complete or partial remission of the nephrotic syndrome

End point description:

To assess whether Eculizumab therapy may achieve persistent, either complete (defined as 24-hour urinary protein excretion reduction to<0,3 grams for adults and <4mg/h/m2 for children) or partial (defined as 24 hour urinary protein excretion reduction to<3,5grams with at least 50% reduction from baseline for adults or <40mg/h/m2 with at least 50% reduction from baseline for children) remission of the nephrotic syndrome.

End point type	Secondary

End point timeframe:

Complete or partial remission of the nephrotic syndrome after the 2 year of Eculizumab treatment

End point values	Eculizumab first 1-year	Eculizumab washout period	Eculizumab second 1-year	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: Patient				
Complete remission of the nephrotic syndrome	0	0	0	
Partial remission of the nephrotic syndrome	3	0	3	
No remission of the nephrotic syndrome	7	10	7	

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on complement Markers

End point title	The Effect of Eculizumab on complement Markers

End point description:

To assess the effect of Eculizumab therapy on markers of complement activity (C3, C4, C3a, C5a, Bb and sC5b9). The measurable unit of sC5b-9 is ng/mL and for C3 and C4 are mg/dL

End point type	Secondary

End point timeframe:

Normalization (reduction to <303 ng/ml) of sC5b-9 and C3, C4 in plasma levels after the first 1-year of Eculizumab and the second 1-year

End point values	Eculizumab first 1-year	Eculizumab second 1-year		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: ng/mL and mg/dL				
median (inter-quartile range (Q1-Q3))				
sC5b-9 12 week	345 (264 to 396)	221 (161 to 238)		
sC5b-9 24 week	289 (225 to 377)	142 (119 to 252)		
sC5b-9 36 week	206 (132 to 418)	203 (139 to 312)		
sC5b-9 48 week	188 (147 to 262)	149 (128 to 194)		
C3 12 week	13.8 (9.8 to 15.5)	13.4 (11.9 to 22.3)		
C3 24 week	13.1 (8.8 to 18.7)	13.5 (12.0 to 16.9)		
C3 36 week	11.7 (9.8 to 15.1)	12.5 (11.2 to 19.1)		
C3 48 week	13.8 (11.3 to 15.4)	11.1 (9.6 to 16.0)		
C4 12 week	15.2 (14.2 to 28.6)	19 (15.0 to 27.8)		
C4 24 week	19.8 (14.6 to 26.4)	18.4 (13.6 to 27.5)		
C4 36 week	17.5 (12.1 to 23.2)	18.5 (12.8 to 27.1)		
C4 48 week	17 (12.9 to 23.2)	15.8 (11.3 to 17.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on complement Markers after the washout period

End point title	The Effect of Eculizumab on complement Markers after the washout period

End point description:

To assess the effect of Eculizumab therapy on markers of complement activity (C3, C4, C3a, C5a, Bb and sC5b9). The measurable unit of sC5b-9 is ng/mL and for C3 and C4 are mg/dL

End point type	Secondary

End point timeframe:

After the washout period compared to the end of the first 1-year Eculizumab treatment

End point values	Eculizumab washout period			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng/mL and mg/dL				
median (inter-quartile range (Q1-Q3))				
sC5b-9	2.118 (1.723 to 2.635)			
C3	20.6 (11.7 to 31.2)			
C4	18.5 (14.3 to 26.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on clinical parameters and laboratory values

End point title	The Effect of Eculizumab on clinical parameters and laboratory values

End point description:

Changes in Body weight (Kg), BMI (kg/m2), Systolic and Diastolic Bp (mm Hg), Total Cholesterol, HDL, LDL and Triglycerides (Mg/dL), LDL:HDL (Ratio), Glucose, hemoglobin (g/dL), Ca (Mg/dL) PO4- (mg/dL), Protein (g/dL) and Albumin (g/dL)

End point type	Secondary

End point timeframe:

During the first1-year and second 1-year of Eculizumab treatment. (without considering the washout period)

End point values	Eculizumab first 1-year	Eculizumab second 1-year		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: kg, Kgm2, mm Hg				
arithmetic mean (standard deviation)				
Body weight 24 week	58.1 (± 12)	61.2 (± 10)		
Body weight 48 week	59.6 (± 11)	61.1 (± 9)		
BMI 24 week	20.9 (± 2.8)	21.6 (± 2.5)		
BMI 48 week	21.3 (± 2.8)	21.8 (± 2.6)		
Systolic BP 24 week	115.9 (± 16)	118.6 (± 11)		
Systolic BP 48 week	118.4 (± 13)	115.2 (± 14)		
Diastolic BP 24 week	72.4 (± 10)	75.4 (± 9)		
Diastolic BP 48 week	74.5 (± 15)	71.4 (± 9)		
Total cholesterol 24 week	184 (± 43)	221.2 (± 63)		
Total cholesterol 48 week	215 (± 83)	214.3 (± 66)		

LDL 24 week	111.9 (± 50)	140.7 (± 52)		
LDL 48 week	135.6 (± 76)	134.4 (± 58)		
LDL:HDL 24 week	2.53 (± 1.4)	3.81 (± 2)		
LDL:HDL 48 week	3.26 (± 2.4)	3.35 (± 2)		
Glucose 24 week	93.5 (± 17)	86.5 (± 9.1)		
Glucose 48 week	87.7 (± 7.9)	86.6 (± 6.4)		
Hemoglobin 24 week	11.3 (± 1.9)	11.6 (± 1.6)		
Hemoglobin 48 week	11.7 (± 2.1)	11.5 (± 1.7)		
Calcium 24 week	8.52 (± 0.3)	8.31 (± 0.4)		
Calcium 48 week	8.52 (± 0.3)	8.28 (± 0.4)		
Phosphorous 24 week	4.84 (± 0.5)	5.08 (± 0.8)		
Phosphorous 48 week	5.05 (± 0.7)	4.92 (± 0.6)		
Potassium 24 week	4.51 (± 0.4)	4.5 (± 0.6)		
Potassium 48 week	4.46 (± 0.3)	4.56 (± 0.8)		
Protein 24 week	5.18 (± 0.4)	4.93 (± 0.9)		
protein 48 week	4.92 (± 0.6)	4.71 (± 0.9)		
Albumin 24 week	2.72 (± 0.3)	2.55 (± 0.6)		
Albumin 48 week	2.65 (± 0.4)	2.48 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on clinical parameters and laboratory value after the washout period

End point title	The Effect of Eculizumab on clinical parameters and laboratory value after the washout period

End point description:

Changes in Body weight (Kg), BMI (kg/m2), Systolic and Diastolic Bp (mm Hg), Total Cholesterol, HDL, LDL and Triglycerides (Mg/dL), LDL:HDL (Ratio), Glucose, hemoglobin (g/dL), Ca (Mg/dL) PO4- (mg/dL), Protein (g/dL) and Albumin (g/dL)

End point type	Secondary

End point timeframe:

After the washout period compared to the end of the first 1-year Eculizumab treatment

End point values	Eculizumab washout period			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Kg, mg/dl				
arithmetic mean (standard deviation)				
Body weight	63.0 (± 10)			
BMI	22.1 (± 2.8)			
Systolic BP	125.0 (± 16)			
Diastolic BP	77.5 (± 17)			
Total Cholesterol	241.7 (± 51)			
LDL	146.7 (± 48)			
HDL	48.3 (± 19)			

LDL:HDL	3.91 (± 2.3)			
Glucose	90.6 (± 7.2)			
Hemoglobin	11.3 (± 1.8)			
Calcium	8.26 (± 0.4)			
Phosphorous	5.43 (± 0.9)			
Potassium	4.83 (± 0.5)			
Protein	4.64 (± 0.9)			
Albumin	2.48 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on Glomerular Filtration Rate (GFR)

End point title	The Effect of Eculizumab on Glomerular Filtration Rate (GFR)

End point description:

Changes in mGFR (mL/min/1.73m2 - by iohexol plasma clearance), eGFR (mL/min/1.73m2 - MDRD)

End point type	Secondary

End point timeframe:

During the first1-year and second 1-year of Eculizumab treatment. (without considering the washout period)

End point values	Eculizumab first 1-year	Eculizumab second 1-year		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)				
mGFR 24 week	83.3 (± 43.9)	71.2 (± 48.6)		
mGFR48 week	87.4 (± 55.1)	76.6 (± 44.1)		
eGFR 24 week	149.4 (± 101.3)	123.5 (± 84)		
eGFR 48 week	136.9 (± 87.1)	119.3 (± 75.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on Glomerular Filtration Rate (GFR) after the washout period

End point title	The Effect of Eculizumab on Glomerular Filtration Rate (GFR) after the washout period

End point description:

Changes in mGFR (mL/min/1.73m2 - by iohexol plasma clearance), eGFR (mL/min/1.73m2 - MDRD)

End point type	Secondary

End point timeframe:

After the washout period compared to the end of the first 1-year Eculizumab treatment

End point values	Eculizumab washout period			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)				
mGFR	75.8 (± 42.7)			
eGFR	120.0 (± 90.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on kidney function

End point title	The Effect of Eculizumab on kidney function

End point description:

Changes in Albuminuria (µg/min), Natriuresis (mEq/24h), Phosphaturia (mg/24h), Urinary urea (g/24H), Albumin fractional clearance (x10-5 mL/min) and IgG fractional clearance (x10-5 mL/min)

End point type	Secondary

End point timeframe:

During the first1-year and second 1-year of Eculizumab treatment. (without considering the washout period)

End point values	Eculizumab first 1-year	Eculizumab second 1-year		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: µg/min and x10-5 mL/min				
median (inter-quartile range (Q1-Q3))				
Albuminuria 24 week	1.920 (1.386 to 2.020)	3.391 (1.903 to 3.969)		
Albuminuria 48 week	2.685 (1.707 to 3.773)	3.461 (0.998 to 3.921)		
Natriuresis 24 week	138 (124 to 162)	156 (96 to 194)		
Natriuresis 48 week	140 (109 to 164)	119 (99 to 152)		
Phosphaturia 24 week	607 (550 to 736)	544 (479 to 691)		
Phosphaturia 48 week	508 (428 to 776)	570 (505 to 683)		
Urinary Urea 24 week	17.3 (15.1 to 22.9)	15.8 (14.2 to 19.2)		

Urinary Urea 48 week	15.4 (14.0 to 20.5)	15.2 (14.4 to 17.4)		
Albumin fractional clearance 24 week	85 (60 to 140)	252 (61 to 449)		
Albumin fractional clearance 48 week	171 (25 to 264)	352 (42 to 685)		
IgG fractional clearance 24 week	14.6 (12.7 to 28.4)	59.2 (12.4 to 137.7)		
IgG fractional clearance 48 week	32 (4.9 to 68.1)	121.6 (6.4 to 320.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Effect of Eculizumab on kidney function after the washout period

End point title	The Effect of Eculizumab on kidney function after the washout period

End point description:

Changes in Albuminuria (µg/min), Natriuresis (mEq/24h), Phosphaturia (mg/24h), Urinary urea (g/24H), Albumin fractional clearance (x10-5 mL/min) and IgG fractional clearance (x10-5 mL/min)

End point type	Secondary

End point timeframe:

After the washout period compared to the end of the first 1-year Eculizumab treatment

End point values	Eculizumab washout period			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/min				
median (inter-quartile range (Q1-Q3))				
Albuminuria	2.839 (1.891 to 4.491)			
Natriuresis	163 (132 to 173)			
Phosphaturia	608 (539 to 625)			
Urinary urea	16.5 (16.2 to 17.3)			
Albumin fractional clearance	243 (93 to 436)			
IgG fractional clearance	50.3 (16.9 to 148.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events will be reported during whole study up to 30 days after last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Eculizumab

Reporting group description: -

Serious adverse events	Eculizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Infusional headache with blurred vision and hemianopia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Impacted tooth			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acquired hydrocele			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

End stage renal disease			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epididymal cyst and varicocele			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression with suicide attempt			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumococcal pneumonia with transient renal function deterioration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis with transient renal function impairment			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious mononucleosis with pulmonary involvement			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Eculizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Bening monoclonal hypergammaglobulinaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
General disorders and administration site conditions Chest pain and nausea subjects affected / exposed occurrences (all) Fever or flu-like symptoms subjects affected / exposed occurrences (all) Peripheral edema subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 5 / 10 (50.00%) 8 5 / 10 (50.00%) 7		
Reproductive system and breast disorders Endometritis, Uterine polyp subjects affected / exposed occurrences (all) Gynaecomastia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection or bronchitis subjects affected / exposed occurrences (all) Allergic rhinitis subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 7 / 10 (70.00%) 15 2 / 10 (20.00%) 2 1 / 10 (10.00%) 1		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injury, poisoning and procedural complications Head injury subjects affected / exposed occurrences (all) Thermal burn subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Cerebral cyst subjects affected / exposed occurrences (all)	 6 / 10 (60.00%) 7 1 / 10 (10.00%) 1		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Eye disorders Headache and blurred vision subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1		
Gastrointestinal disorders			

Gastroenteritis or vomiting subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 7		
Upper abdominal pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Generalized pruritus subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Acne subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Renal and urinary disorders Renal function deterioration with hyperuricaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Endocrine disorders Secondary hyperparathyroidism subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms/ contraction subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3		
Back or neck pain subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Rhabdomyolysis or increased serum creatinine phosphokinase subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Infections and infestations			

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 4		
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Hypocalcemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Metabolic acidosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Dehydration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hypovitaminosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2015	The results of the interim analyzes indicated that patients suffering from membranoproliferative glomerulonephritis with nephrotic syndrome and complement activation benefited considerably of Eculizumab treatment during the first year. The evidence that proteinuria and other parameters tend to return to levels prior to the patient's entry into the study after stopping treatment, not only constitutes evidence of the causal relationship between treatment and the observed changes, but suggeststed that Eculizumab could be used as a long-term therapy in these patients. On the basis of these observations we proposed a substantial urgent amendment so that patients who complete the first 12 months of Eculizumab treatment continue the treatment (four weekly infusions of Eculizumab 900 mg in the phase of induction and infusions of Eculizumab 1200 mg every two weeks in the phase of maintenance) for another twelve months. Alexion is available to continue to provide the necessary medication free of charge. After treatment suspension, patients will be followed for another three months (recovery phase).

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/30929851