Clinical trial results:
Safety in Haemolytic PNH Patients Treated with Eculizumab: A Multi-center Open-label Research Design Study (SHEPHERD)

Summary

EudraCT number	2004-002795-42
Trial protocol	SE IE DE GB IT ES
Global end of trial date	18 October 2006

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	C04-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00122304
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Incorporated
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 1 47 10 06 06, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +33 1 47 10 06 06, 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	Final
Date of interim/final analysis	06 January 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2006
Global end of trial reached?	Yes
Global end of trial date	18 October 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety of eculizumab in patients with transfusion-dependent haemolytic paroxysmal nocturnal haemoglobinuria (PNH)

Protection of trial subjects:

Patients must have been vaccinated for Neisseria meningitidis 14 days prior to randomisation.

Background therapy: -

Evidence for comparator:

No comparator was used in this trial.

Actual start date of recruitment	16 December 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	97
EEA total number of subjects	64

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)	0
Adults (18-64 years)	90
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 33 clinical sites in Australia, Belgium, Canada, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, United States and the United Kingdom participated and enrolled patients in this study.

Pre-assignment

Screening details:

Subjects who had at least one transfusion in the 2 years prior to screening, and were meeting all of the inclusion/exclusion criteria were eligible to enter this study. 107 subjects were screened, 97 were enrolled and received eculizumab.

Pre-assignment period milestones

Number of subjects started	97
Number of subjects completed	97

Period 1

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

Blinding implementation details:

Not applicable (open-label study)

Arms

Arm title	eculizumab

Arm description:

During the Induction Period, patients received 600 mg of eculizumab IV once a week for 4 doses, followed by 900 mg eculizumab IV 1 week later for 1 dose. During the Maintenance Period, patients received 900 mg eculizumab IV every 2 weeks for approximately 24 doses. Each dose was administered by IV infusion over a 25- to 45-minute period.

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:

600 mg of eculizumab once a week for 4 weeks, followed by 900 mg of eculizumab 1 week later for 1 dose, then 900 mg of eculizumab every 2 weeks up through 52 weeks.

Number of subjects in period 1	eculizumab
Started	97
Completed	96
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	eculizumab
Reporting group description:	
During the Induction Period, patients received 600 mg of eculizumab IV once a week for 4 doses, followed by 900 mg eculizumab IV 1 week later for 1 dose. During the Maintenance Period, patients received 900 mg eculizumab IV every 2 weeks for approximately 24 doses. Each dose was administered by IV infusion over a 25- to 45-minute period.	

Reporting group values	eculizumab	Total	
Number of subjects	97	97	
Age categorical Units: Subjects			
Adults (18-64 years)	90	90	
65 to 75 years	5	5	
Superior or equal to 75 year old	2	2	
Age continuous Units: years			
median	41		
inter-quartile range (Q1-Q3)	29 to 51	-	
Gender categorical Units: Subjects			
Female	49	49	
Male	48	48	
Race Units: Subjects			
Caucasian	88	88	
Asian	3	3	
Black	3	3	
Other	3	3	
Blood Type Units: Subjects			
A-	10	10	
A+	31	31	
B-	3	3	
B+	5	5	
AB-	1	1	
AB+	5	5	
O-	6	6	
O+	36	36	
Weight Units: kilogram(s)			
median	73.5		
inter-quartile range (Q1-Q3)	62.8 to 81.1	-	
Height Units: centimeters			
median	173		
inter-quartile range (Q1-Q3)	163 to 180	-	
Haemoglobin prior to transfusion			

Units: gram(s)/deciliter			
median	7.5		
inter-quartile range (Q1-Q3)	6.9 to 8.3	-	
Haemoglobin after transfusion			
Units: gram(s)/deciliter			
median	9.4		
inter-quartile range (Q1-Q3)	8.2 to 10.1	-	
Number of packed red blood cell (RBC) units transfused			
Units: Number of units			
median	8		
inter-quartile range (Q1-Q3)	4 to 24	-	

End points

End points reporting groups

Reporting group title	eculizumab

Reporting group description:

During the Induction Period, patients received 600 mg of eculizumab IV once a week for 4 doses, followed by 900 mg eculizumab IV 1 week later for 1 dose. During the Maintenance Period, patients received 900 mg eculizumab IV every 2 weeks for approximately 24 doses. Each dose was administered by IV infusion over a 25- to 45-minute period.

Primary: Intravascular haemolysis measured by LDH AUC

End point title	Intravascular haemolysis measured by LDH AUC[1]

End point description:

A quantitative assessment of haemolysis was obtained by calculating the AUC for LDH from Baseline to Week 52, and the data were analysed using a Wilcoxon signed rank test.

End point type	Primary

End point timeframe:

Through week 52

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	97			
Units: U/L × day				
median (full range (min-max))	-632264 (-1788824 to -74498)			

Statistical analyses

No statistical analyses for this end point

Secondary: Levels of fatigue

End point title	Levels of fatigue

End point description:

The Quality-of-Life (QoL) instrument FACIT-Fatigue scale version 4 was utilised to collect QoL data. The scoring guideline for the FACIT-Fatigue scale version 4 instrument was used to calculate the QoL score; per the corresponding scoring guideline, scores can range from 0 to 52, with higher scores indicating improvement in fatigue. Data reported indicate change of FACIT-Fatigue Scores Between Baseline at several time points.

End point type	Secondary

End point timeframe:

The FACIT-Fatigue SCALE was administered through 52 weeks.

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: QoL score				
arithmetic mean (standard error)				
Baseline	30.8 (± 1.2)			
Change from baseline at Wk 1	5.6 (± 1)			
Change from baseline at Wk 2	7.1 (± 0.98)			
Change from baseline at Wk 3	9.1 (± 1.1)			
Change from baseline at Wk 4	8.9 (± 1.12)			
Change from baseline at Wk 12	9.9 (± 1.2)			
Change from baseline at Wk 26	11.8 (± 1.2)			
Change from baseline at Wk 52	12.2 (± 1.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intravascular haemolysis measured as change in LDH from baseline

End point title	Intravascular haemolysis measured as change in LDH from baseline

End point description:

Data reported describe change of lactate dehydrogenase (LDH) values from Baseline to selected time points through 52 Weeks.

End point type	Secondary

End point timeframe:

Through 52 weeks.

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: U/L				
arithmetic mean (standard error)				
Baseline	2200.7 (± 104.9)			
Week 1	-1519.5 (± 87.05)			
Week 2	-1794.4 (± 100.71)			
Week 3	-1895.4 (± 102.86)			
Week 4	-1901.2 (± 103.87)			

Week 12	-1811.2 (± 111.19)			
Week 26	-1869.4 (± 109.33)			
Week 52	-1908.7 (± 105.11)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Information regarding AEs was collected from the time the patient signed the informed consent form up to 30 days after the last dose of eculizumab was administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	7

Reporting groups

Reporting group title	eculizumab

Reporting group description: -

Serious adverse events	eculizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 97 (19.59%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Rib fracture			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolism			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			

subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic cerebral infarction				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 97 (2.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 97 (3.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Haemolysis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anaemia macrocytic				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paroxysmal nocturnal haemoglobinuria				

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal insufficiency			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 97 (1.03%)		
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 %

Non-serious adverse events	eculizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 97 (97.94%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	51 / 97 (52.58%)		
occurrences (all)	94		
Dizziness			
subjects affected / exposed	14 / 97 (14.43%)		
occurrences (all)	18		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 97 (19.59%)		
occurrences (all)	27		
Influenza-like illness			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	11		
Oedema peripheral			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	7		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	20 / 97 (20.62%)		
occurrences (all)	39		
Diarrhoea			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	15		
Abdominal pain			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	35		
Constipation			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	16		

Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 12		
Cough subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 6		
Bronchitis subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 5		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	7 / 97 (7.22%) 9		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 10		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	15 / 97 (15.46%) 19		
Arthralgia subjects affected / exposed occurrences (all)	12 / 97 (12.37%) 15		
Myalgia subjects affected / exposed occurrences (all)	10 / 97 (10.31%) 15		
Pain in extremity subjects affected / exposed occurrences (all)	8 / 97 (8.25%) 10		
Muscle cramp subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 8		
Neck pain subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 6		

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	31 / 97 (31.96%)		
occurrences (all)	44		
Upper respiratory tract infection			
subjects affected / exposed	29 / 97 (29.90%)		
occurrences (all)	35		
Urinary tract infection			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	15		
Herpes simplex			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	11		
Viral infection			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Gastroenteritis			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2005	The purpose of this global amendment was to broaden the study population and to identify a primary surrogate endpoint for efficacy, namely lactate dehydrogenase as area under the curve.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported