Clinical trial results:
AN OPEN-LABEL MULTI-CENTER STUDY OF ECULIZUMAB IN CHILDREN AND ADOLESCENTS WITH A DIAGNOSIS OF PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

Summary

EudraCT number	2009-010402-11
Trial protocol	Outside EU/EEA
Global end of trial date	12 May 2011

Results information

Result version number	v1 (current)
This version publication date	06 August 2016
First version publication date	06 August 2016

Trial information

Trial identification

Sponsor protocol code	M07-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00867932
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Incorporated
Sponsor organisation address	100 College Street, New Haven, United States, CT 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)	EMEA-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	04 November 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2011
Global end of trial reached?	Yes
Global end of trial date	12 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Study M07-005 was to evaluate the PK and PD parameter estimates of eculizumab to confirm the dose regimens for paediatric patients with PNH

Protection of trial subjects:

Patients must have been vaccinated against Neisseria meningitidis, Pneumococcus species, and Hemophilus influenzae type b at least 14 days prior to the start of study drug, or be vaccinated and receive treatment with appropriate antibiotics until 14 days after vaccination. Patients were excluded for prior treatment with eculizumab, presence or suspicion of bacterial infection or recurrent bacterial infections, or history of meningococcal, pneumococcal, or gonococcal disease. Patients were also excluded if pregnant, breastfeeding, or intending to conceive during the study period.

Background therapy:

No background therapy was used in this trial.

Evidence for comparator:

No comparator was used in this trial.

Actual start date of recruitment	02 October 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	7
EEA total number of subjects	0

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)	1
Adolescents (12-17 years)	6
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period lasted from October 2009 to January 2011. Three sites in the USA enrolled a total of 7 patients.

Pre-assignment

Screening details:

Screening phase was approx. 2 weeks. ICF and paediatric/adolescent assent forms were signed at or before Visit 1. Inclusion/exclusion criteria were obtained and evaluated. If all screening criteria are met, the patient was eligible to enter the treatment phase of the study after receiving a N. meningitidis, pneumococcus and hemophilus vaccination

Period 1

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

Arms

Arm title	eculizumab

Arm description:

All 7 patients enrolled in the trial received eculizumab. There is no other arm in the trial.

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:

- If weight ≥30 kg:
Induction loading: 600mg weekly x 4
Maintenance: 900mg Wk5; 900mg Q2wks

- If weight 20 - <30kg:
Induction/loading: 600mg weekly x 2
Maintenance: 600mg Wk3; 600mg Q2wks

- If weight 10 - <20kg:
Induction/loading: 600mg weekly x 1
Maintenance: 300mg Wk2; 300mg Q2wks

- If weight 5 – <10 kg:
Induction/loading: 300 mg Weekly for 1 Week
Maintenance: 300mg Wk2; 300mg Q3wks

Eculizumab was administered via a 35 minutes (+/-10 minutes) intravenous infusion.

Number of subjects in period 1	eculizumab
Started	7
Induction Phase	7
Maintenance Phase	7
Completed	7

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Seven patients aged 11–17 years were enrolled between October 2009 and January 2011; younger patients did not present for eligibility screening at the participating centers during the study period. All patients entered the body weight cohort of greater or equal to 30 kg. Each patient received all nine doses of eculizumab via peripheral vein and completed the study period of 12 weeks.	

Reporting group values	Treatment	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
Children (2-11 years)	1	1	
Adolescents (12-17 years)	6	6	
Age continuous Units: years			
arithmetic mean	15.01		
standard deviation	± 2.2779	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	3	3	
LDH			
LDH was collected during screening period and then at all visits during induction period, at visits 8 and 10 during maintenance period, at early termination visit and all visits during follow-up for early termination, as applicable.			
Units: Subjects			
Enrolled patients	7	7	
Hematology			
Hb was collected for all patients at several time points durign the study			
Units: Subjects			
Enrolled patients	7	7	

End points

End points reporting groups

Reporting group title	eculizumab

Reporting group description:

All 7 patients enrolled in the trial received eculizumab. There is no other arm in the trial.

Primary: PK and PD evaluation

End point title	PK and PD evaluation[1]

End point description:

PD response was measured by the capacity of patient serum to lyse chicken erythrocytes in a human serum-complement hemolytic assay; complete complement blockade was defined as <20% hemolysis in vitro. All baseline trough plasma levels of eculizumab were undetectable. Peak and trough eculizumab concentrations increased gradually and reached a plateau by week 4. At week 12, median trough eculizumab levels were 192.5 mcg/ml (range 124.2-321.1) and median peak levels were 425.4 mcg/ml (range 220.5-556.1). The max and min conc. of eculizumab, and AUC were significantly associated with the change from baseline in LDH at the follow-up visits (P=0.0273, P=0.0250 and P=0.0263 respectively). Prior start of eculizumab, in vitro hemolysis of <20%, that is, inducing complete complement blockade, after steady-state levels were reached at week 4.

End point type	Primary

End point timeframe:

PK ad PD samples were collected before and after completing the administration of eculizumab at each visit.

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	7			
Units: mcg/ml				
median (full range (min-max))				
Median trough at week 12	192.5 (124.2 to 321.1)			
Median peak at week 12	425.4 (220.5 to 556.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Examination of treatment-emergent adverse events

End point type	Secondary

End point timeframe:

12 weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Number of AE				
Patients with at least one TEAE	7			
Patients with no TEAE	0			
Patients with any serious TEAE	2			
Total number of TEAE	69			
Mild severity	4			
Moderate severity	1			
Severe severity	2			
unrelated (relationship)	2			
possible (relationship)	3			
probable (relationship)	2			
Definite (relationship)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - Mean change of LDH from baseline at week 12

End point title	Efficacy - Mean change of LDH from baseline at week 12

End point description:

The area under the curve (AUC) for the change of LDH from baseline (week 0 to week 12) was also calculated.

End point type	Secondary

End point timeframe:

12 weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: U*Day/L				
number (not applicable)				
Mean LDH AUC of change from baseline	-60634			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - Mean Plasma-free Haemoglobin

End point title	Efficacy - Mean Plasma-free Haemoglobin

End point description:

Plasma-free haemoglobin levels were analyzed at 12 weeks.

End point type	Secondary

End point timeframe:

12 weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: milligram(s)/dl				
number (not applicable)				
Mean plasma-free haemoglobin conc. (baseline)	17.7			
Mean plasma-free haemoglobin conc. (week 12)	7.44			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - LDH values and change of LDH from baseline

End point title	Efficacy - LDH values and change of LDH from baseline

End point description:

Efficacy summary of LDH values and change of LDH from baseline.

End point type	Secondary

End point timeframe:

12 weeks

End point values	eculizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: U/L				
number (not applicable)				
Mean change from baseline (week 1)	-672			
Mean change from baseline (week 2)	-763			
Mean change from baseline (week 3)	-752			
Mean change from baseline (week 4)	-761			
Mean change from baseline (week 8)	-747			
Mean change from baseline (week 12)	-771			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time patient signs the informed consent form up to 8 weeks after last dose of eculizumab

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) that occurred in at least 2 subjects during the study are reported here. TEAEs are defined as an event not present prior to exposure to eculizumab or any event already present that worsens in either intensity or frequency following exposure to eculizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	All participating patients in the trial

Reporting group description: -

Serious adverse events	All participating patients in the trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Aplastic anaemia			
alternative dictionary used: MedDRA 14.1			

subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Menorrhagia				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Acute sinusitis				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site cellulitis				
alternative dictionary used: MedDRA 14.1				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media acute				
alternative dictionary used: MedDRA 14.1				

subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All participating patients in the trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain upper			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Infections and infestations			
Upper respiratory tract infection			
alternative dictionary used: MedDRA 14.1			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2010	Amendment 2 (protocol v3.0): Modify the protocol to restrict inclusion criteria as agreed in the Paediatric Investigation Plan for eculizumab. Further to the evaluation of the Paediatric Investigation Plan for eculizumab by the European Paediatric Committee, the protocol inclusion criteria was modified as follows: 1. To update dosing for patients 2 - 17 years old and weight ≥5kg. 2. To include vaccination requirements previously described in the methodology section of the protocol as an inclusion requirement. In addition, to add vaccination requirements for Pneumococci and Haemophilus. 3. To only include paediatric patients in whom haemolysis contributes to the anaemia. 4. To not include patients with history of meningococcal/pneumococcal/gonococcal disease. 5. To add an external data monitoring committee (DMC) to monitor safety. 6. To add an exploratory endpoint to assess correlation between LDH and PNH clone size.

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/24777716