Clinical trial results:
EVIDENCE - EVALUATION OF POTENTIAL PREDICTORS OF DISEASE PROGRESSION IN PATIENTS WITH aHUS, INCLUDING GENETICS, BIOMARKERS, AND TREATMENT

Summary

EudraCT number	2015-003135-35
Trial protocol	DE BE GB IT
Global end of trial date	05 October 2017

Results information

Result version number	v1 (current)
This version publication date	10 August 2018
First version publication date	10 August 2018

Trial information

Trial identification

Sponsor protocol code	ECU-aHUS-403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02614898
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc
Sponsor organisation address	1-15 Avenue Edouard Belin, Rueil-Malmaison, France,
Public contact	European Clinical Trial Information, Alexion Europe SAS , +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS , +33 147100606, 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	05 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2017
Global end of trial reached?	Yes
Global end of trial date	05 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a prospective, open-label study with no participant randomization. Treatment for aHUS was observational and at the discretion of the treating physician. The purpose of this study was to assess disease manifestations of complement-mediated thrombotic microangiopathy (TMA) and evaluate potential clinical predictors of disease manifestations and progression in participants with aHUS with or without eculizumab treatment in the clinical setting.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
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	United States: 19
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	67
EEA total number of subjects	20

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)	1
Children (2-11 years)	12
Adolescents (12-17 years)	2

Adults (18-64 years)	43
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sixty-seven participants were enrolled in this study (15 paediatric and 52 adults).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paediatric

Arm description:

Participants with atypical hemolytic uremic syndrome (aHUS) who were less than 18 years at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.

Arm type	Paediatric
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosing regimen was solely at the discretion of the treating physician.

Arm title	Adult

Arm description:

Participants with aHUS who were 18 years or older at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.

Arm type	Adult
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosing regimen was solely at the discretion of the treating physician.

Number of subjects in period 1	Paediatric	Adult
Started	15	52
Safety Population	15	52
Completed	0	1
Not completed	15	51
Physician Decision	1	8
Other, Additional Information Unavailable	-	11
Lost to Follow-up	-	2
Withdrawal by Parent/Guardian	1	1
Withdrawal by Subject	-	2
Study Terminated by Sponsor	3	-
Missing	-	1
Participated until study termination	10	26

Baseline characteristics

Reporting groups	
Reporting group title	Paediatric
Reporting group description:	
Participants with atypical hemolytic uremic syndrome (aHUS) who were less than 18 years at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.	
Reporting group title	Adult
Reporting group description:	
Participants with aHUS who were 18 years or older at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.	

Reporting group values	Paediatric	Adult	Total
Number of subjects	15	52	67
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	1	0	1
Children (2-11 years)	12	0	12
Adolescents (12-17 years)	2	0	2
Adults (18-64 years)	0	43	43
From 65-84 years	0	9	9
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.9	43.3	
standard deviation	± 3.46	± 17.26	-
Gender categorical Units: Subjects			
Female	6	34	40
Male	9	18	27
Race/Ethnicity Units: Subjects			
Caucasian	12	44	56
Asian	1	2	3
Black	1	5	6
Other	1	1	2

End points

End points reporting groups

Reporting group title	Paediatric

Reporting group description:

Participants with atypical hemolytic uremic syndrome (aHUS) who were less than 18 years at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.

Reporting group title	Adult

Reporting group description:

Participants with aHUS who were 18 years or older at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.

Primary: Rate of TMA Manifestations During Eculizumab Treatment Compared to Off-Treatment

End point title	Rate of TMA Manifestations During Eculizumab Treatment Compared to Off- Treatment[1]

End point description:

TMA is defined as one of following: Hematologic or renal events due to aHUS; Extra-renal clinical signs and symptoms of aHUS; Tissue (for example, kidney transplant) biopsy demonstrating TMA.

Sample data were collected, but as the study was terminated before the planned number of participants were enrolled, primary outcome analysis was not performed.

End point type	Primary

End point timeframe:

Up to 47 Months

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: Sample data were collected, but as the study was terminated before the planned number of participants were enrolled, primary outcome analysis was not performed. Therefore, no statistical analysis has been specified.

End point values	Paediatric	Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: N/A				
number (not applicable)				

Notes:

[2] - Study terminated before planned number of participants were enrolled; no primary outcome analysis.
[3] - Study terminated before planned number of participants were enrolled; no primary outcome analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To 24 Months In Estimated Glomerular Filtration Rate (eGFR)

End point title	Change From Baseline To 24 Months In Estimated Glomerular Filtration Rate (eGFR)

End point description:

Change in estimated Glomerular Filtration Rate (eGFR) over time using the chronic kidney disease-epidemiology formula

Sample data were collected, but as the study was terminated before the planned number of participants were enrolled, primary outcome analysis was not performed.

End point type	Secondary

End point timeframe:

Baseline, 24 Months

End point values	Paediatric	Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: N/A				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - Study terminated before planned number of participants were enrolled; no primary outcome analysis.
[5] - Study terminated before planned number of participants were enrolled; no primary outcome analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Plasma Exchange and Plasma Infusion (PE/PI)

End point title	Incidence of Plasma Exchange and Plasma Infusion (PE/PI)

End point description:

The number of occurrences of PE/PI per participant-years was calculated and summarized by treatment status.

Sample data were collected, but as the study was terminated before the planned number of participants were enrolled, primary outcome analysis was not performed.

End point type	Secondary

End point timeframe:

Up to 47 Months

End point values	Paediatric	Adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: N/A				

Notes:

[6] - Study terminated before planned number of participants were enrolled; no primary outcome analysis.
[7] - Study terminated before planned number of participants were enrolled; no primary outcome analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Day 0 through Month 24, or until participant was discontinued from the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Paediatric

Reporting group description:

Participants with aHUS who were less than 18 years at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.

Reporting group title	Adult

Reporting group description:

Participants with aHUS who were 18 years or older at baseline and who initiated treatment with eculizumab prior to study entry. Dosing regimen changed solely at the discretion of the treating physician.

Serious adverse events	Paediatric	Adult	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	14 / 52 (26.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula occlusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis streptococcal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticulitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Paediatric	Adult	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	31 / 52 (59.62%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiolipoma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Skin cancer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	6 / 52 (11.54%)	
occurrences (all)	1	7	
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	6	
Thrombophlebitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Venous thrombosis limb			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	7 / 52 (13.46%)	
occurrences (all)	0	8	
Catheter site erythema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Chest pain			

subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	3	
Extravasation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	6 / 52 (11.54%)	
occurrences (all)	0	7	
Feeling hot			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Hypothermia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	3	
Peripheral swelling			
subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Temperature intolerance			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Amenorrhoea			

subjects affected / exposed[1]	0 / 6 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Breast cyst			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	6	
Epistaxis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 52 (0.00%)	
occurrences (all)	8	0	
Nasal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Wheezing			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Confusional state			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 15 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	6	
Investigations			
Blood calcium increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 15 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	6	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	3	
Blood magnesium decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Bone density decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Faecal calprotectin increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Faecal elastase concentration decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Haptoglobin decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Liver function test increased			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Red blood cell schistocytes present			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Anal injury			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Corneal abrasion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Procedural dizziness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Procedural nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Procedural pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Wound			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Dizziness postural			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 15 (6.67%)	10 / 52 (19.23%)	
occurrences (all)	1	11	
Hypotonia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Migraine			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Poor quality sleep			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Somnolence			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 52 (1.92%)	
occurrences (all)	1	3	
Increased tendency to bruise			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nephrogenic anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Inner ear inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Eye colour change			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Eye disorder			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Ocular icterus			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Orbital oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	6 / 52 (11.54%)	
occurrences (all)	0	7	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	4	
Abdominal tenderness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Anal incontinence			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Anorectal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Bowel movement irregularity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Chronic gastritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	

Crohn's disease			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Dental caries			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	7 / 52 (13.46%)	
occurrences (all)	0	10	
Duodenal ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Enterocolitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Faeces discoloured			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastric ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Gastrointestinal disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastrointestinal erosion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Large intestine polyp			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	

Malabsorption			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Mouth haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	11 / 52 (21.15%)	
occurrences (all)	0	12	
Pancreatitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	
Abdominal distension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Actinic keratosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Blister			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Neurodermatitis			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Onychoclasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Renal impairment			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Renal tubular acidosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	3	
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Flank pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Joint swelling			

subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Osteopenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Infections and infestations			
Aeromonas infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Catheter site infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Cytomegalovirus infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	4	

Escherichia urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	3	
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Lower respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Pseudomonas infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Staphylococcal infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Tonsillitis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	

Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	11 / 52 (21.15%)	
occurrences (all)	1	18	
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	4	
Varicella zoster virus infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Viral pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Vulvovaginal candidiasis			
subjects affected / exposed[2]	0 / 6 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hypokalaemia			

subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	4	
Hypomagnesaemia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	2	
Metabolic acidosis			
subjects affected / exposed	0 / 15 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 15 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The AE of Amenorrhoea can only affect females.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The AE of Vulvovaginal candidiasis can only affect females.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2015	• Clarified the definitions around laboratory criteria to be monitored and reported in the event of a potential thrombotic microangiopathy (TMA), based on requests from key opinion leaders (KOLs) and internal discussions
17 November 2016	• Revised patient reported outcome (PRO) data collection (added European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life [QLQ] C30, reduced frequency of measurement) • Removed the volume or dilution of serum that lyses 50% of erythrocytes (CH50) and anti-drug antibody (ADA) measurements and reduced free complement component 5 (C5) collection frequency to correspond with pharmacokinetics testing • Removed all physical exams with the exception of baseline • Clarification and refinement of coding requirements for future research on biochemical samples

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As the study was terminated for administrative reasons, before enrollment was complete, the efficacy analyses were not performed.

Notes: