# 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<br>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<br>Units: years | | | |
| arithmetic mean | 7.9 | 43.3 | |
| standard deviation | ± 3.46 | ± 17.26 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 34 | 40 |
| Male | 9 | 18 | 27 |
| Race/Ethnicity<br>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)<br>• 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<br>• Removed all physical exams with the exception of baseline<br>• 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: