



## Clinical trial results:

### AN OPEN-LABEL, MULTI-CENTER CONTROLLED CLINICAL TRIAL OF ECULIZUMAB IN ADOLESCENT PATIENTS WITH PLASMA THERAPY-SENSITIVE ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS)

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2008-006955-28       |
| Trial protocol           | DE NL SE AT ES GB IT |
| Global end of trial date | 10 October 2013      |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 24 July 2016 |
| First version publication date | 24 July 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | C08-003B |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                            |
|------------------------------------|----------------------------|
| ISRCTN number                      | -                          |
| ClinicalTrials.gov id (NCT number) | NCT00844428                |
| WHO universal trial number (UTN)   | -                          |
| Other trial identifiers            | BB-IND 11075: BB-IND 11075 |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Alexion Pharmaceuticals Incorporated   |
| Sponsor organisation address | 352 Knotter Drive, Cheshire, CT, United States, 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)       | 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                       | 29 December 2013 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 10 October 2013  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 10 October 2013  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the effect of eculizumab on TMA-Event Free status defined as the absence for at least 12 weeks of [1] decrease in platelet count of >25% from the Platelet Count Pre-PT Baseline Set-Point; [2] PT while the patient is receiving eculizumab, or [3] new dialysis

Protection of trial subjects:

Vaccination against N. meningitidis at least 14 days prior to study drug initiation or prophylactic antibiotics protection until 2 weeks after vaccination

Background therapy: -

Evidence for comparator:

Each patient served as his/her own control

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 24 July 2009     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 5 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 3    |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | France: 9         |
| Country: Number of subjects enrolled | Germany: 1        |
| Country: Number of subjects enrolled | Canada: 2         |
| Country: Number of subjects enrolled | Italy: 1          |
| Country: Number of subjects enrolled | Sweden: 1         |
| Worldwide total number of subjects   | 20                |
| EEA total number of subjects         | 18                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |    |
|--|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 5  |
| Adults (18-64 years)                     | 15 |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Results from Study C08-003A were combined with results from another study, Study C08-003B. Study C08-003A was conducted in adults (n=15) and Study C08-003B was conducted in adolescents (n=5; EudraCT No.: 2008-006955-28). Combined results from these 2 studies are reported here.

### Pre-assignment

Screening details:

Patients receiving PT for aHUS and observed to receive  $\geq 1$  PT every two weeks, and no more than 3 PT treatments/week for at least 8 weeks before the first dose of eculizumab. Patients who met the eligibility criteria during the Observation Period were enrolled into the Treatment Period which commenced with the first eculizumab dose.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 23 <sup>[1]</sup> |
| Number of subjects completed | 20                |

### Pre-assignment subject non-completion reasons

|                            |                   |
|----------------------------|-------------------|
| Reason: Number of subjects | Screen failure: 3 |
|----------------------------|-------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.  
Justification: Period 1 is the observation period during which baseline is assessed.

### Period 1

|                              |                              |
|------------------------------|------------------------------|
| Period 1 title               | Observation Period (8 Weeks) |
| Is this the baseline period? | No                           |
| Allocation method            | Not applicable               |
| Blinding used                | Not blinded                  |

### Arms

|           |             |
|-----------|-------------|
| Arm title | Observation |
|-----------|-------------|

Arm description:

During the 8-week Observation Period, clinical laboratory testing, platelet counts, hemolytic markers, pro-thrombotic measures, pro-inflammatory markers, complement markers, and samples for renal function measures were collected on a weekly basis. Adverse events were also recorded on a weekly basis during the 8-week Observation Period. Additionally, all PT sessions administered to the patient during the Observation Period were recorded

|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| Number of subjects in period 1 | Observation |
|--------------------------------|-------------|
| Started                        | 20          |
| Completed                      | 20          |

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**Period 2**

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Treatment Period (26 Weeks) |
| Is this the baseline period? | Yes <sup>[2]</sup>          |
| Allocation method            | Not applicable              |
| Blinding used                | Not blinded                 |

**Arms**

|                  |            |
|------------------|------------|
| <b>Arm title</b> | eculizumab |
|------------------|------------|

## Arm description:

All patients received open-label eculizumab administered intravenously on the following dose schedule: Induction dose - 900 mg per week for four weeks and a dose of 1200 mg one week later; Maintenance dose - 1200 mg every two weeks. Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg within one hour before plasma infusion or within one hour after the completion of each plasma exchange.

The intent-to-treat (ITT) population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses. For both the efficacy and safety analyses, all 20 patients who were treated with study drug were included in the ITT population.

|  |                                       |
|--|---------------------------------------|
| 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:

Induction dose - 900 mg per week for four weeks and a dose of 1200 mg one week later  
Maintenance dose - 1200 mg every two weeks

Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg within one hour before plasma infusion or within one hour after the completion of each plasma exchange.

## Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The post-treatment period only applies to the patients who discontinued treatment. There are 5 patients who were off drug at end of study.

|                                       |            |
|---------------------------------------|------------|
| <b>Number of subjects in period 2</b> | eculizumab |
| Started                               | 20         |
| Completed                             | 20         |

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**Period 3**

|                              |                            |
|------------------------------|----------------------------|
| Period 3 title               | Extension Treatment Period |
| Is this the baseline period? | No                         |
| Allocation method            | Not applicable             |
| Blinding used                | Not blinded                |

## Arms

|  |                                       |
|--|---------------------------------------|
| Arm title                              | long-term eculizumab                  |
| Arm description: -                     |                                       |
| 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:

Induction dose - 900 mg per week for four weeks and a dose of 1200 mg one week later

Maintenance dose - 1200 mg every two weeks

Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg within one hour before plasma infusion or within one hour after the completion of each plasma exchange.

| Number of subjects in period 3 <sup>[3]</sup> | long-term eculizumab |
|---|----------------------|
| Started                                       | 19                   |
| Completed                                     | 18                   |
| Not completed                                 | 1                    |
| Death   | 1                    |

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All analyses summarize results from pooled data of 2 protocols: C08-003A and C08-003B. One adolescent patient (from study C08-003B) discontinued from the study after 26 weeks.

## Period 4

|                              |   |
|------------------------------|---|
| Period 4 title               | Post-treatment period (discontinuation) |
| Is this the baseline period? | No                                      |
| Allocation method            | Not applicable                          |
| Blinding used                | Not blinded                             |

## Arms

|  |                 |
|--|-----------------|
| Arm title  | eculizumab      |
| Arm description:   |                 |
| Patients who discontinued eculizumab during the study were required to have follow-up visits. These assessments were performed at 1 week, 2 weeks, 4 weeks, and 8 weeks after the last dose of eculizumab. |                 |
| Arm type   | No intervention |
| No investigational medicinal product assigned in this arm  |                 |

| <b>Number of subjects in period 4<sup>[4]</sup></b> | eculizumab |
|---|------------|
| Started   | 5          |
| Completed   | 4          |
| Not completed                                       | 1          |
| Adverse event, serious fatal                        | 1          |

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Notes:

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The worldwide number enrolled in the trial do not include screen failure.

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | eculizumab |
|-----------------------|------------|

Reporting group description:

All patients received open-label eculizumab administered intravenously on the following dose schedule: Induction dose - 900 mg per week for four weeks and a dose of 1200 mg one week later; Maintenance dose - 1200 mg every two weeks. Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg within one hour before plasma infusion or within one hour after the completion of each plasma exchange.

The intent-to-treat (ITT) population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses. For both the efficacy and safety analyses, all 20 patients who were treated with study drug were included in the ITT population.

| Reporting group values                    | eculizumab | Total |  |
|---|------------|-------|--|
| Number of subjects                        | 20         | 20    |  |
| Age categorical<br>Units: Subjects        |            |       |  |
| Adolescents (12-17 years)                 | 5          | 5     |  |
| Adults (18-64 years)                      | 15         | 15    |  |
| Age continuous<br>Units: years            |            |       |  |
| arithmetic mean                           | 32.3       |       |  |
| standard deviation                        | ± 14.92    | -     |  |
| Gender categorical<br>Units: Subjects     |            |       |  |
| Female                                    | 12         | 12    |  |
| Male                                      | 8          | 8     |  |
| Race<br>Units: Subjects                   |            |       |  |
| American Indian or Alaska Native          | 0          | 0     |  |
| Asian                                     | 0          | 0     |  |
| Native Hawaiian or Other Pacific Islander | 0          | 0     |  |
| Black or African American                 | 2          | 2     |  |
| White                                     | 18         | 18    |  |
| More than one race                        | 0          | 0     |  |
| Unknown or Not Reported                   | 0          | 0     |  |
| Platelet Category<br>Units: Subjects      |            |       |  |
| < 150 x10 <sup>9</sup> /L                 | 3          | 3     |  |
| ≥ 150 x10 <sup>9</sup> /L                 | 17         | 17    |  |
| LDH Category<br>Units: Subjects           |            |       |  |
| > ULN                                     | 4          | 4     |  |
| ≤ ULN                                     | 16         | 16    |  |
| eGFR category<br>Units: Subjects          |            |       |  |
| < 15                                      | 4          | 4     |  |
| 15 ≤ 30                                   | 6          | 6     |  |



|  |          |   |  |
|--|----------|---|--|
| 30 ≤ 45                                      | 6        | 6 |  |
| 45 ≤ 60                                      | 2        | 2 |  |
| 60 ≤ 90                                      | 2        | 2 |  |
| CKD<br>Units: Subjects                       |          |   |  |
| Stage 2                                      | 2        | 2 |  |
| Stage 3a                                     | 2        | 2 |  |
| Stage 3b                                     | 6        | 6 |  |
| Stage 4                                      | 6        | 6 |  |
| Stage 5                                      | 4        | 4 |  |
| Platelet Count<br>Units: x10 <sup>9</sup> /L |          |   |  |
| arithmetic mean                              | 227.98   |   |  |
| standard deviation                           | ± 77.658 | - |  |
| LDH<br>Units: U/l                            |          |   |  |
| arithmetic mean                              | 222.6    |   |  |
| standard deviation                           | ± 69.88  | - |  |
| Creatinine<br>Units: micromole(s)/litre      |          |   |  |
| arithmetic mean                              | 286.9    |   |  |
| standard deviation                           | ± 215.44 | - |  |
| eGFR<br>Units: mL/min/1.73*m <sup>2</sup>    |          |   |  |
| arithmetic mean                              | 30.9     |   |  |
| standard deviation                           | ± 19.01  | - |  |

## End points

### End points reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Observation |
|-----------------------|-------------|

Reporting group description:

During the 8-week Observation Period, clinical laboratory testing, platelet counts, hemolytic markers, pro-thrombotic measures, pro-inflammatory markers, complement markers, and samples for renal function measures were collected on a weekly basis. Adverse events were also recorded on a weekly basis during the 8-week Observation Period. Additionally, all PT sessions administered to the patient during the Observation Period were recorded

|                       |            |
|-----------------------|------------|
| Reporting group title | eculizumab |
|-----------------------|------------|

Reporting group description:

All patients received open-label eculizumab administered intravenously on the following dose schedule: Induction dose - 900 mg per week for four weeks and a dose of 1200 mg one week later; Maintenance dose - 1200 mg every two weeks. Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg within one hour before plasma infusion or within one hour after the completion of each plasma exchange.

The intent-to-treat (ITT) population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses. For both the efficacy and safety analyses, all 20 patients who were treated with study drug were included in the ITT population.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | long-term eculizumab |
|-----------------------|----------------------|

Reporting group description: -

|                       |            |
|-----------------------|------------|
| Reporting group title | eculizumab |
|-----------------------|------------|

Reporting group description:

Patients who discontinued eculizumab during the study were required to have follow-up visits. These assessments were performed at 1 week, 2 weeks, 4 weeks, and 8 weeks after the last dose of eculizumab.

### Primary: Proportion of Patients With TMA Event-free Status

|                 |  |
|-----------------|--|
| End point title | Proportion of Patients With TMA Event-free Status <sup>[1]</sup> |
|-----------------|--|

End point description:

TMA Event-free status is defined as the absence for at least 12 weeks of [1] decrease in platelet count of > 25% from the Platelet Count Pre-PT Baseline Set Point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Through 26 weeks

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 does not support statistical analyses for single arm trial.

| End point values                  | eculizumab      |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 80 (56 to 94)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of Patients With Hematologic Normalization

|                 |  |
|-----------------|--|
| End point title | Proportion of Patients With Hematologic Normalization <sup>[2]</sup> |
|-----------------|--|

End point description:

Hematologic Normalization was defined as normalization of both platelet count and lactic dehydrogenase (LDH) sustained for at least two consecutive measurements which spanned a period of at least four weeks.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Through 26 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study is a single arm trial and the system does not support statistical analyses for single arm trial.

| End point values                  | eculizumab      |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 90 (68 to 99)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of Patients With Complete TMA Response

|                 |  |
|-----------------|--|
| End point title | Proportion of Patients With Complete TMA Response <sup>[3]</sup> |
|-----------------|--|

End point description:

The proportion of patients who achieved a Complete TMA Response from baseline through 26 weeks of treatment with eculizumab was determined. Complete TMA Response was defined as Hematologic Normalization plus improvement in renal function (defined as  $\geq 25\%$  reduction from baseline in serum creatinine), which was sustained for two consecutive measurements over a period of at least four weeks.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Through 26 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study is a single arm trial and the system does not support statistical analyses for single arm trial.

| End point values                  | eculizumab      |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 25 (9 to 49)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: TMA Intervention Rate

|                 |                       |
|-----------------|-----------------------|
| End point title | TMA Intervention Rate |
|-----------------|-----------------------|

End point description:

TMA Intervention Rate (# PE/PI and # Dialysis Events/Patient/Day) in the eculizumab treatment period (from baseline through 26 weeks) for PE/PI and (from the fifteenth day following the first eculizumab dose through 26 weeks) for new dialysis events was compared with the TMA Intervention Rate during the pre-eculizumab treatment period.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through 26 weeks

| End point values                     | eculizumab      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 20              |  |  |  |
| Units: #events/patient/day           |                 |  |  |  |
| arithmetic mean (standard deviation) | 0 ( $\pm$ 0)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Platelet Count Change From Baseline to 26 Weeks

|                 |   |
|-----------------|---|
| End point title | Platelet Count Change From Baseline to 26 Weeks |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to 26 Weeks

|  |                        |  |  |  |
|--|------------------------|--|--|--|
| <b>End point values</b>                      | eculizumab             |  |  |  |
| Subject group type                           | Reporting group        |  |  |  |
| Number of subjects analysed                  | 20                     |  |  |  |
| Units: 10 <sup>9</sup> cells/L               |                        |  |  |  |
| least squares mean (confidence interval 95%) | 6.75 (-15.73 to 29.23) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients With Platelet Count Normalization

|  |  |
|--|--|
| End point title  | Proportion of Patients With Platelet Count Normalization |
| End point description:<br>Platelet count normalization was defined as the platelet count observed to be $\geq 150 \times 10^9/L$ on at least 2 consecutive measurements which span a period of at least 4 weeks. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Through 26 Weeks   |  |

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | eculizumab      |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 90 (68 to 99)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients With TMA Event-free Status

|   |   |
|---|---|
| End point title   | Proportion of Patients With TMA Event-free Status |
| End point description:<br>TMA Event-free status is defined as the absence for at least 12 weeks of [1] decrease in platelet count of > 25% from the Platelet Count Pre-PT Baseline Set Point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Through End of Study, Median Exposure 156 Weeks   |   |

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | eculizumab      |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 95 (75 to 100)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients With Hematologic Normalization

|   |   |
|---|---|
| End point title   | Proportion of Patients With Hematologic Normalization |
| End point description:<br>Hematologic Normalization was defined as normalization of both platelet count and lactic dehydrogenase (LDH) sustained for at least two consecutive measurements which spanned a period of at least four weeks. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Through End of Study, Median Exposure 156 Weeks   |   |

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | eculizumab      |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 90 (68 to 99)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients With Complete TMA Response

|   |   |
|---|---|
| End point title   | Proportion of Patients With Complete TMA Response |
| End point description:<br>The proportion of patients who achieved a Complete TMA Response from baseline through end of study with eculizumab was determined. Complete TMA Response was defined as Hematologic Normalization plus improvement in renal function (defined as $\geq 25\%$ reduction from baseline in serum creatinine), which was sustained for two consecutive measurements over a period of at least four weeks. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Through End of Study, Median Exposure 156 Weeks   |   |

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | eculizumab      |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 55 (32 to 77)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: TMA Intervention Rate

|  |                       |
|--|-----------------------|
| End point title  | TMA Intervention Rate |
| End point description:<br>TMA Intervention Rate (# PE/PI and # Dialysis Events/Patient/Day) in the eculizumab treatment period (from baseline through end of study) for PE/PI and (from the 15th day following the first eculizumab dose through end of study) for new dialysis events was compared with the TMA Intervention Rate during the pre-eculizumab treatment period. |                       |
| End point type   | Secondary             |
| End point timeframe:<br>Through End of Study, Median Exposure 156 Weeks  |                       |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | eculizumab      |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 20              |  |  |  |
| Units: #events/patient/day           |                 |  |  |  |
| arithmetic mean (standard deviation) | 0 ( $\pm$ 0.02) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Platelet Count Change From Baseline to 156 Weeks

|  |  |
|--|--|
| End point title                                    | Platelet Count Change From Baseline to 156 Weeks |
| End point description:                             |  |
| End point type                                     | Secondary  |
| End point timeframe:<br>From Baseline to 156 Weeks |  |

|  |                         |  |  |  |
|--|-------------------------|--|--|--|
| <b>End point values</b>                      | eculizumab              |  |  |  |
| Subject group type                           | Reporting group         |  |  |  |
| Number of subjects analysed                  | 20                      |  |  |  |
| Units: 10 <sup>9</sup> cells/L               |                         |  |  |  |
| least squares mean (confidence interval 95%) | -3.68 (-25.15 to 17.79) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Patients With Platelet Count Normalization

|  |  |
|--|--|
| End point title  | Proportion of Patients With Platelet Count Normalization |
| End point description:<br>Platelet count normalization was defined as the platelet count observed to be $\geq 150 \times 10^9/L$ on at least 2 consecutive measurements which span a period of at least 4 weeks. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Through End of Study, Median Exposure 156 Weeks  |  |

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | eculizumab      |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 20              |  |  |  |
| Units: Percentage of Participants |                 |  |  |  |
| number (confidence interval 95%)  | 90 (68 to 99)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration

|   |  |
|---|--|
| End point title   | Pharmacokinetics (PK) and Pharmacodynamics (PD); Minimum and Maximum Blood Concentration |
| End point description:<br>PK parameters C <sub>min</sub> and C <sub>max</sub> were estimated using a population PK model developed from the observed PK concentration data. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Induction Phase for 4 weeks followed by Maintenance Phase starting on Week 5 through 26 weeks or longer.  |  |



|   |                  |  |  |  |
|---|------------------|--|--|--|
| <b>End point values</b>                   | eculizumab       |  |  |  |
| Subject group type                        | Reporting group  |  |  |  |
| Number of subjects analysed               | 20               |  |  |  |
| Units: microgram(s)/millilitre            |                  |  |  |  |
| arithmetic mean (standard deviation)      |                  |  |  |  |
| max concentration during induction period | 161.47 (± 27.29) |  |  |  |
| max concentration during maintenance      | 427.48 (± 67.54) |  |  |  |
| min concentration during induction period | 112.43 (± 16.98) |  |  |  |
| min concentration during maintenance      | 212.45 (± 53.75) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Through end of study; Exposure to eculizumab in this study extended for a median of 156 weeks and ranged from 26 weeks to 182 weeks.

Adverse event reporting additional description:

At every visit, patients were asked a standard non-leading question to elicit any changes in their medical well-being including inquiry about any hospitalization, accidents, and new or changed concomitant medication regimens. AEs were also documented from any data collected (e.g. laboratory values, physical examination findings, ECG changes, etc.).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | eculizumab |
|-----------------------|------------|

Reporting group description:

All patients received open-label eculizumab administered intravenously on the following dose schedule: Induction dose - 900 mg per week for four weeks and a dose of 1200 mg one week later; Maintenance dose - 1200 mg every two weeks. Patients who received plasma exchange or infusion during the eculizumab treatment period received a supplemental dose of 600 mg within one hour before plasma infusion or within one hour after the completion of each plasma exchange.

| Serious adverse events  | eculizumab       |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 13 / 20 (65.00%) |  |  |
| number of deaths (all causes)                                       | 1                |  |  |
| number of deaths resulting from adverse events                      |                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Renal cell carcinoma  |                  |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders  |                  |  |  |
| Hypotension   |                  |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vein disorder   |                  |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Venous thrombosis limb                               |                |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgical and medical procedures                      |                |  |  |
| Catheter removal                                     |                |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Limb operation                                       |                |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Medical device complication                          |                |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Transplant rejection                                 |                |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Amyloidosis  |                |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Investigations                                       |                |  |  |
| Electrocardiogram T wave inversion                   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Hip fracture                                    |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Humerus fracture                                |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tendon rupture                                  |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Pericardial effusion                            |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Headache  |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Impaired gastric emptying                       |                |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Rash  |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Haematuria                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure chronic                           |                 |  |  |
| subjects affected / exposed                     | 2 / 20 (10.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Osteoarthritis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bacteraemia                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Clostridium difficile colitis                   |                 |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Enterococcal infection                          |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastroenteritis norovirus                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hepatitis E                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Influenza                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Localised infection                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Peritonitis                                     |                 |  |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 2 / 20 (10.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Post procedural infection                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%)  |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pyelonephritis                                  |                 |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Q fever   |                |  |  |
| subjects affected / exposed                     | 1 / 20 (5.00%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | eculizumab        |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events               |                   |  |  |
| subjects affected / exposed   | 20 / 20 (100.00%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Angiomyolipoma  |                   |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Benign breast neoplasm  |                   |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Lipoma  |                   |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Melanocytic naevus  |                   |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Skin papilloma  |                   |  |  |
| subjects affected / exposed   | 3 / 20 (15.00%)   |  |  |
| occurrences (all)   | 3                 |  |  |
| Squamous cell carcinoma   |                   |  |  |
| subjects affected / exposed   | 1 / 20 (5.00%)    |  |  |
| occurrences (all)   | 1                 |  |  |
| Vascular disorders  |                   |  |  |
| Arterial haemorrhage  |                   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Arterial occlusive disease                           |                 |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Haematoma  |                 |  |  |
| subjects affected / exposed                          | 2 / 20 (10.00%) |  |  |
| occurrences (all)                                    | 2               |  |  |
| Haemorrhage  |                 |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Hypertension   |                 |  |  |
| subjects affected / exposed                          | 9 / 20 (45.00%) |  |  |
| occurrences (all)                                    | 9               |  |  |
| Hypotension  |                 |  |  |
| subjects affected / exposed                          | 4 / 20 (20.00%) |  |  |
| occurrences (all)                                    | 4               |  |  |
| Orthostatic hypotension                              |                 |  |  |
| subjects affected / exposed                          | 2 / 20 (10.00%) |  |  |
| occurrences (all)                                    | 2               |  |  |
| Vein disorder  |                 |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Venous thrombosis                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Surgical and medical procedures                      |                 |  |  |
| Arteriovenous fistula operation                      |                 |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Hip arthroplasty                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| General disorders and administration site conditions |                 |  |  |



|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Asthenia                    |                 |  |  |
| subjects affected / exposed | 4 / 20 (20.00%) |  |  |
| occurrences (all)           | 4               |  |  |
| Chest pain                  |                 |  |  |
| subjects affected / exposed | 2 / 20 (10.00%) |  |  |
| occurrences (all)           | 2               |  |  |
| Extravasation               |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Fatigue                     |                 |  |  |
| subjects affected / exposed | 4 / 20 (20.00%) |  |  |
| occurrences (all)           | 4               |  |  |
| Hypothermia                 |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Infusion site extravasation |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Infusion site swelling      |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Injection site haematoma    |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Localised oedema            |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Malaise                     |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Medical device complication |                 |  |  |
| subjects affected / exposed | 2 / 20 (10.00%) |  |  |
| occurrences (all)           | 2               |  |  |
| Oedema                      |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 6 / 20 (30.00%)<br>6 |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Polyp<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 7 / 20 (35.00%)<br>7 |  |  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 20 (20.00%)<br>4 |  |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Reproductive system and breast disorders<br>Breast swelling<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  |  |  |
| Menorrhagia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 20 (10.00%)<br>2 |  |  |
| Oedema genital<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Ovarian cyst<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)    | 7 / 20 (35.00%)<br>7 |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| Dyspnoea                           |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Epistaxis                          |                 |  |  |
| subjects affected / exposed        | 3 / 20 (15.00%) |  |  |
| occurrences (all)                  | 3               |  |  |
| Lung consolidation                 |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Nasal congestion                   |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Oropharyngeal pain                 |                 |  |  |
| subjects affected / exposed        | 4 / 20 (20.00%) |  |  |
| occurrences (all)                  | 4               |  |  |
| Productive cough                   |                 |  |  |
| subjects affected / exposed        | 2 / 20 (10.00%) |  |  |
| occurrences (all)                  | 2               |  |  |
| Pulmonary congestion               |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Rhinorrhoea                        |                 |  |  |
| subjects affected / exposed        | 3 / 20 (15.00%) |  |  |
| occurrences (all)                  | 3               |  |  |
| Upper respiratory tract congestion |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Psychiatric disorders              |                 |  |  |
| Affective disorder                 |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Anxiety                            |                 |  |  |
| subjects affected / exposed        | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Depression                         |                 |  |  |

|                                       |                 |  |  |
|---------------------------------------|-----------------|--|--|
| subjects affected / exposed           | 3 / 20 (15.00%) |  |  |
| occurrences (all)                     | 3               |  |  |
| Insomnia                              |                 |  |  |
| subjects affected / exposed           | 2 / 20 (10.00%) |  |  |
| occurrences (all)                     | 2               |  |  |
| Investigations                        |                 |  |  |
| Basophil count increased              |                 |  |  |
| subjects affected / exposed           | 2 / 20 (10.00%) |  |  |
| occurrences (all)                     | 2               |  |  |
| Blood creatine increased              |                 |  |  |
| subjects affected / exposed           | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                     | 1               |  |  |
| Blood creatinine increased            |                 |  |  |
| subjects affected / exposed           | 4 / 20 (20.00%) |  |  |
| occurrences (all)                     | 4               |  |  |
| Blood lactate dehydrogenase increased |                 |  |  |
| subjects affected / exposed           | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                     | 1               |  |  |
| Blood parathyroid hormone increased   |                 |  |  |
| subjects affected / exposed           | 2 / 20 (10.00%) |  |  |
| occurrences (all)                     | 2               |  |  |
| Blood potassium increased             |                 |  |  |
| subjects affected / exposed           | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                     | 1               |  |  |
| Blood pressure abnormal               |                 |  |  |
| subjects affected / exposed           | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                     | 1               |  |  |
| Cardiac murmur                        |                 |  |  |
| subjects affected / exposed           | 2 / 20 (10.00%) |  |  |
| occurrences (all)                     | 2               |  |  |
| Electrocardiogram T wave inversion    |                 |  |  |
| subjects affected / exposed           | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                     | 1               |  |  |
| Eosinophil count increased            |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Glomerular filtration rate decreased           |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Haptoglobin increased                          |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Low density lipoprotein increased              |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Monocyte count increased                       |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Platelet count decreased                       |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Reticulocyte count increased                   |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Weight decreased                               |                 |  |  |
| subjects affected / exposed                    | 3 / 20 (15.00%) |  |  |
| occurrences (all)                              | 3               |  |  |
| White blood cell count increased               |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| White blood cells urine positive               |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Injury, poisoning and procedural complications |                 |  |  |
| Ankle fracture                                 |                 |  |  |
| subjects affected / exposed                    | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Arteriovenous fistula site complication        |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Contusion                   |                 |  |  |
| subjects affected / exposed | 4 / 20 (20.00%) |  |  |
| occurrences (all)           | 4               |  |  |
| Corneal abrasion            |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Excoriation                 |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Foreign body                |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Head injury                 |                 |  |  |
| subjects affected / exposed | 2 / 20 (10.00%) |  |  |
| occurrences (all)           | 2               |  |  |
| Hip fracture                |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Humerus fracture            |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Ligament sprain             |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Limb injury                 |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Scratch                     |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Wound                       |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Wrist fracture              |                 |  |  |

|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  |  |  |
| Congenital, familial and genetic disorders<br>Dermoid cyst<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  |  |  |
| Cardiac disorders<br>Hypertensive heart disease<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Nervous system disorders<br>Cerebral haematoma<br>subjects affected / exposed<br>occurrences (all)<br><br>Cerebral microangiopathy<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Myoclonus<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Paresis<br>subjects affected / exposed<br>occurrences (all)<br><br>Somnolence | 1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1<br><br>3 / 20 (15.00%)<br>3<br><br>11 / 20 (55.00%)<br>11<br><br>1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1<br><br>1 / 20 (5.00%)<br>1 |  |  |

|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Syncope                              |                 |  |  |
| subjects affected / exposed          | 2 / 20 (10.00%) |  |  |
| occurrences (all)                    | 2               |  |  |
| Blood and lymphatic system disorders |                 |  |  |
| Abnormal clotting factor             |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Anaemia folate deficiency            |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Anaemia                              |                 |  |  |
| subjects affected / exposed          | 7 / 20 (35.00%) |  |  |
| occurrences (all)                    | 7               |  |  |
| Iron deficiency anaemia              |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Leukopenia                           |                 |  |  |
| subjects affected / exposed          | 3 / 20 (15.00%) |  |  |
| occurrences (all)                    | 3               |  |  |
| Lymph node pain                      |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Lymphadenopathy                      |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Lymphopenia                          |                 |  |  |
| subjects affected / exposed          | 2 / 20 (10.00%) |  |  |
| occurrences (all)                    | 2               |  |  |
| Microcytosis                         |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Splenomegaly                         |                 |  |  |
| subjects affected / exposed          | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                    | 1               |  |  |



|   |                      |  |  |
|---|----------------------|--|--|
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Ear and labyrinth disorders<br>Deafness bilateral<br>subjects affected / exposed<br>occurrences (all)           | 1 / 20 (5.00%)<br>1  |  |  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)  | 2 / 20 (10.00%)<br>2 |  |  |
| Motion sickness<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  |  |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)   | 4 / 20 (20.00%)<br>4 |  |  |
| Eye disorders<br>Eye irritation Conjunctival<br>haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  |  |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1  |  |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                | 5 / 20 (25.00%)<br>5 |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 2 / 20 (10.00%)<br>2   |  |  |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1    |  |  |
| Abdominal rigidity<br>subjects affected / exposed<br>occurrences (all)   | 1 / 20 (5.00%)<br>1    |  |  |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 20 (15.00%)<br>3   |  |  |
| Ascites<br>subjects affected / exposed<br>occurrences (all)              | 1 / 20 (5.00%)<br>1    |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 3 / 20 (15.00%)<br>3   |  |  |
| Crohn's disease<br>subjects affected / exposed<br>occurrences (all)      | 1 / 20 (5.00%)<br>1    |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 10 / 20 (50.00%)<br>10 |  |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)           | 1 / 20 (5.00%)<br>1    |  |  |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)    | 1 / 20 (5.00%)<br>1    |  |  |
| Gingival hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1    |  |  |
| Gingival ulceration<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1    |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Haemorrhoids                |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Impaired gastric emptying   |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Malaena                     |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Nausea                      |                  |  |  |
| subjects affected / exposed | 10 / 20 (50.00%) |  |  |
| occurrences (all)           | 10               |  |  |
| Subileus                    |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Tooth impacted              |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Umbilical hernia            |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Vomiting                    |                  |  |  |
| subjects affected / exposed | 10 / 20 (50.00%) |  |  |
| occurrences (all)           | 10               |  |  |
| Medical device pain         |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Chest discomfort            |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Hepatobiliary disorders     |                  |  |  |
| Cholelithiasis              |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Hepatocellular injury       |                  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Skin and subcutaneous tissue disorders |                 |  |  |
| Alopecia                               |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Blister                                |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Dermatitis                             |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Ecchymosis                             |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Eczema                                 |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Erythema                               |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Heat rash                              |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Hyperhidrosis                          |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Pruritus                               |                 |  |  |
| subjects affected / exposed            | 3 / 20 (15.00%) |  |  |
| occurrences (all)                      | 3               |  |  |
| Psoriasis                              |                 |  |  |
| subjects affected / exposed            | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                      | 1               |  |  |
| Rash                                   |                 |  |  |
| subjects affected / exposed            | 4 / 20 (20.00%) |  |  |
| occurrences (all)                      | 4               |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Rash macular<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>1  |  |  |
| Skin disorder<br>subjects affected / exposed<br>occurrences (all)       | 1 / 20 (5.00%)<br>1  |  |  |
| Skin fissures<br>subjects affected / exposed<br>occurrences (all)       | 1 / 20 (5.00%)<br>1  |  |  |
| Renal and urinary disorders   |                      |  |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1  |  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 20 (5.00%)<br>2  |  |  |
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 20 (5.00%)<br>1  |  |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)         | 1 / 20 (5.00%)<br>1  |  |  |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)         | 1 / 20 (5.00%)<br>1  |  |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all)       | 1 / 20 (5.00%)<br>1  |  |  |
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)    | 3 / 20 (15.00%)<br>3 |  |  |
| Renal failure acute<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  |  |  |
| Endocrine disorders   |                      |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Adrenal insufficiency<br>subjects affected / exposed<br>occurrences (all)      | 1 / 20 (5.00%)<br>1  |  |  |
| Musculoskeletal and connective tissue disorders                                |                      |  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 20 (15.00%)<br>3 |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 6 / 20 (30.00%)<br>6 |  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 20 (5.00%)<br>1  |  |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 20 (10.00%)<br>2 |  |  |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 20 (5.00%)<br>1  |  |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)             | 1 / 20 (5.00%)<br>1  |  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)              | 4 / 20 (20.00%)<br>4 |  |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)          | 2 / 20 (10.00%)<br>2 |  |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 20 (5.00%)<br>1  |  |  |
| Neck pain  |                      |  |  |

|                                     |                 |  |  |
|-------------------------------------|-----------------|--|--|
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Osteoporosis                        |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Pain in extremity                   |                 |  |  |
| subjects affected / exposed         | 4 / 20 (20.00%) |  |  |
| occurrences (all)                   | 4               |  |  |
| Tendon disorder                     |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Tendonitis                          |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Infections and infestations         |                 |  |  |
| Ateriovenous fistula site infection |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| BK virus infection                  |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Bacteraemia                         |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 2               |  |  |
| Bronchitis                          |                 |  |  |
| subjects affected / exposed         | 2 / 20 (10.00%) |  |  |
| occurrences (all)                   | 2               |  |  |
| Cytomegalovirus infection           |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Erythrasma                          |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |
| Escherichia urinary tract infection |                 |  |  |
| subjects affected / exposed         | 1 / 20 (5.00%)  |  |  |
| occurrences (all)                   | 1               |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Fungal infection            |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Fungal skin infection       |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Gastroenteritis             |                  |  |  |
| subjects affected / exposed | 3 / 20 (15.00%)  |  |  |
| occurrences (all)           | 3                |  |  |
| Herpes zoster               |                  |  |  |
| subjects affected / exposed | 3 / 20 (15.00%)  |  |  |
| occurrences (all)           | 3                |  |  |
| Infection                   |                  |  |  |
| subjects affected / exposed | 2 / 20 (10.00%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Influenza                   |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Localised infection         |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Nasopharyngitis             |                  |  |  |
| subjects affected / exposed | 12 / 20 (60.00%) |  |  |
| occurrences (all)           | 12               |  |  |
| Otitis media                |                  |  |  |
| subjects affected / exposed | 2 / 20 (10.00%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Pneumonia                   |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Post procedural infection   |                  |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Sinusitis                   |                  |  |  |
| subjects affected / exposed | 3 / 20 (15.00%)  |  |  |
| occurrences (all)           | 3                |  |  |



|   |                      |  |  |
|---|----------------------|--|--|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 8 / 20 (40.00%)<br>8 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 20 (15.00%)<br>3 |  |  |
| Vaginal infection<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 20 (5.00%)<br>1  |  |  |
| Viral pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 20 (5.00%)<br>1  |  |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 20 (10.00%)<br>2 |  |  |
| Vulvovaginal candidiasis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 20 (5.00%)<br>1  |  |  |
| Metabolism and nutrition disorders  |                      |  |  |
| Acidosis<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 20 (10.00%)<br>2 |  |  |
| Alkalosis<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 20 (5.00%)<br>1  |  |  |
| Cachexia<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 20 (5.00%)<br>1  |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 20 (5.00%)<br>1  |  |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 20 (5.00%)<br>1  |  |  |
| Fluid overload  |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypercalcaemia              |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hyperkalaemia               |                 |  |  |
| subjects affected / exposed | 2 / 20 (10.00%) |  |  |
| occurrences (all)           | 2               |  |  |
| Hyponatraemia               |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Malnutrition                |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Metabolic acidosis          |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Vitamin D deficiency        |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hyperglycaemia              |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hyperuricaemia              |                 |  |  |
| subjects affected / exposed | 1 / 20 (5.00%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Hypokalaemia                |                 |  |  |
| subjects affected / exposed | 2 / 20 (10.00%) |  |  |
| occurrences (all)           | 2               |  |  |
| Musculoskeletal pain        |                 |  |  |
| subjects affected / exposed | 2 / 20 (10.00%) |  |  |
| occurrences (all)           | 2               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 08 September 2009 | Global modification to clinical study protocol, in particular, to: <ul style="list-style-type: none"><li>- provide a justification for the selected dosing regimen in aHUS as compared to the experience with eculizumab in PNH</li><li>- correct the eculizumab dose prior to any FFP intervention based on modeling data</li><li>- update certain entry criteria by adding wash out periods instead of total exclusion based on current standards of care</li><li>- introduce antibiotic coverage for patients that are post transplant and on immunosuppressive treatment and/or aggressive plasma therapy</li><li>- align protocol with European Summary of Product Characteristics, in particular requirements pertaining to contraception methods and hypersensitivity to eculizumab, murine proteins or to excipients</li><li>- define the extension period to allow patients to continue to receive the investigational product while pending access to licensed product</li></ul> |
| 01 September 2010 | Global change to the clinical trial protocol to make some clarifications with regards to the ADAMTS13 activity exclusion cut-off value, and intended statistical tests.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23738544>