



## Clinical trial results:

### Prospective Follow-up Study for Patients who Completed Study ALX0681-C301 (HERCULES) to Evaluate Long-term Safety and Efficacy of Caplacizumab (Post-HERCULES)

#### Summary

EudraCT number	2016-001503-23
Trial protocol	AT ES HU GB CZ BE FR DE NL IT
Global end of trial date	23 October 2020

#### Results information

Result version number	v1
This version publication date	06 November 2021
First version publication date	06 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	LTS16371
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02878603
WHO universal trial number (UTN)	-
Other trial identifiers	Post-HERCULES: ALX0681-C302

Notes:

#### Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly Mazarin Cedex, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	18 December 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 October 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

- To evaluate long-term safety and efficacy of caplacizumab.
- To evaluate safety and efficacy of repeated use of caplacizumab.
- To characterise long-term impact of acquired thrombotic thrombocytopenic purpura (aTTP).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Italy: 7

Worldwide total number of subjects	104
EEA total number of subjects	43

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	95
From 65 to 84 years	9
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at 43 active sites in 13 countries. A total of 104 subjects who completed Study ALX0681-C301 (HERCULES; NCT02553317) were enrolled between 06-October-2016 and 27-October-2017 in this current study: LTS16371 (ALX0681-C302).

### Pre-assignment

Screening details:

Subjects who were randomised to caplacizumab/placebo and received caplacizumab for recurrence of acquired thrombotic thrombocytopenic purpura (aTTP) in ALX0681-C301 were enrolled in Caplacizumab group, and subjects randomised to placebo in ALX0681-C301 were enrolled under Standard of Care (SoC) group in the current study LTS16371.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Standard of Care (Treated in Study C301)

Arm description:

Subjects who completed study ALX0681-C301 with SoC (plasma exchange [PE], corticosteroid and other immunosuppressive agents) treatment were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to investigational medicinal product [IMP], withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg intravenous (IV) dose followed by a daily 10 milligrams (mg) subcutaneous (SC) injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Arm type	Experimental
Investigational medicinal product name	Caplacizumab
Investigational medicinal product code	ALX-0081
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous bolus use , Subcutaneous use

Dosage and administration details:

- First day of treatment: 10 mg IV injection prior to PE followed by a 10 mg SC injection after completion of PE. - Subsequent days of treatment during PE: daily 10 mg SC injection following PE. - Treatment after PE period: daily 10 mg SC injections for 30 days (and eventually 28-day extension period, if needed).

Investigational medicinal product name	SoC treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- PE with plasma (e.g., fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant).
- Corticosteroid treatment.
- Use of other immunosuppressive agents (e.g., rituximab).

<b>Arm title</b>	Caplacizumab (Treated in Study C301)
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Arm description:

Subjects who completed study ALX0681-C301 and received caplacizumab with PE and

immunosuppressive agents were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to IMP, withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg IV dose followed by a daily 10 mg SC injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Arm type	Experimental
Investigational medicinal product name	Caplacizumab
Investigational medicinal product code	ALX-0081
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous bolus use , Subcutaneous use

Dosage and administration details:

- First day of treatment: 10 mg IV injection prior to PE followed by a 10 mg SC injection after completion of PE. - Subsequent days of treatment during PE: daily 10 mg SC injection following PE. - Treatment after PE period: daily 10 mg SC injections for 30 days (and eventually 28-day extension period, if needed).

<b>Number of subjects in period 1</b>	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)
Started	29	75
Completed	23	70
Not completed	6	5
Consent withdrawn by subject	1	1
Physician decision	-	3
Lost to follow-up	4	1
Other (Death)	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Standard of Care (Treated in Study C301)
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Reporting group description:

Subjects who completed study ALX0681-C301 with SoC (plasma exchange [PE], corticosteroid and other immunosuppressive agents) treatment were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to investigational medicinal product [IMP], withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg intravenous (IV) dose followed by a daily 10 milligrams (mg) subcutaneous (SC) injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Reporting group title	Caplacizumab (Treated in Study C301)
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Reporting group description:

Subjects who completed study ALX0681-C301 and received caplacizumab with PE and immunosuppressive agents were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to IMP, withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg IV dose followed by a daily 10 mg SC injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Reporting group values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)	Total
Number of subjects	29	75	104
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	51.5 ± 14.8	46.0 ± 11.9	-
Gender categorical Units: Subjects			
Female	23	51	74
Male	6	24	30
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	13	19
White	21	52	73
More than one race	0	2	2
Unknown or Not Reported	2	5	7

## End points

### End points reporting groups

Reporting group title	Standard of Care (Treated in Study C301)
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Reporting group description:

Subjects who completed study ALX0681-C301 with SoC (plasma exchange [PE], corticosteroid and other immunosuppressive agents) treatment were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to investigational medicinal product [IMP], withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg intravenous (IV) dose followed by a daily 10 milligrams (mg) subcutaneous (SC) injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Reporting group title	Caplacizumab (Treated in Study C301)
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Reporting group description:

Subjects who completed study ALX0681-C301 and received caplacizumab with PE and immunosuppressive agents were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to IMP, withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg IV dose followed by a daily 10 mg SC injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

### Primary: Percentage of Subjects With Acquired Thrombotic Thrombocytopenic Purpura (aTTP-) Related Events

End point title	Percentage of Subjects With Acquired Thrombotic Thrombocytopenic Purpura (aTTP-) Related Events <sup>[1]</sup>
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End point description:

aTTP-related events were defined as: aTTP-related death, recurrence of aTTP (defined as recurrent thrombocytopenia requiring initiation of daily PE) or at least one major thromboembolic event (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis). Percentage of subjects with at least one of aTTP-related events during the study were reported in this endpoint. Analysis was performed on efficacy intention-to-observe (efficacy ITO) population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: percentage of subjects				
number (not applicable)	37.9	8.2		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Acquired Thrombotic Thrombocytopenic Purpura-related Events

End point title	Number of Acquired Thrombotic Thrombocytopenic Purpura-related Events <sup>[2]</sup>
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End point description:

aTTP-related events were defined as: aTTP-related death, recurrence of aTTP (defined as recurrent thrombocytopenia requiring initiation of daily PE) or at least one major thromboembolic event (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis). Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: aTTP-related events	11	4		

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to First Acquired Thrombotic Thrombocytopenic Purpura-related Events

End point title	Time to First Acquired Thrombotic Thrombocytopenic Purpura-related Events <sup>[3]</sup>
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End point description:

Time to first aTTP-related events was defined as the duration of time (in days) from Baseline up to first aTTP-related event in LTS16371. Subjects without an event during LTS16371 were censored at the end of the study. Kaplan-Meier method was used for the analysis. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, '99999' was used as a space filler which indicates that median and 95% confidence interval (CI) data were not calculated due to very few subjects with events.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

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: As the endpoint was descriptive in nature, no statistical analysis was provided.



End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: days				
median (confidence interval 95%)	99999 (845.00 to 99999)	99999 (99999 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With aTTP related Deaths Reported During the Study

End point title	Number of Subjects With aTTP related Deaths Reported During the Study <sup>[4]</sup>
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End point description:

Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[4] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: subjects	1	0		

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Recurrence of Disease (aTTP)

End point title	Percentage of Subjects With Recurrence of Disease (aTTP) <sup>[5]</sup>
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End point description:

Recurrence of aTTP was defined as recurrent thrombocytopenia requiring initiation of daily PE. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[5] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: percentage of subjects				
number (not applicable)	27.6	8.2		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Disease (aTTP) Recurrence Reported During the Study

End point title	Number of Disease (aTTP) Recurrence Reported During the Study <sup>[6]</sup>
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End point description:

Recurrence of aTTP was defined as recurrent thrombocytopenia requiring initiation of daily PE. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[6] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: aTTP recurrence	8	4		

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to Recurrence of Disease (aTTP)

End point title	Time to Recurrence of Disease (aTTP) <sup>[7]</sup>
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End point description:

Time to first recurrence of disease (aTTP) was defined as the duration of time (in days) from Baseline up to first recurrence of aTTP event in LTS16371. Recurrence of aTTP: defined as recurrent thrombocytopenia requiring initiation of daily PE. Subjects without an event during LTS16371 were censored at the end of the study. Kaplan-Meier method was used for the analysis. Analysis was

performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, '99999' was used as a space filler which indicates that median and 95% CI data were not calculated due to very few subjects with events.

End point type	Primary
End point timeframe:	
From Baseline up to 36 months	

Notes:

[7] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: days				
median (confidence interval 95%)	99999 (1280.00 to 99999)	99999 (99999 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Major Thromboembolic Events Including Thrombotic Thrombocytopenic Purpura (TTP)

End point title	Percentage of Subjects With Major Thromboembolic Events Including Thrombotic Thrombocytopenic Purpura (TTP) <sup>[8]</sup>
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End point description:

Major thromboembolic events (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep venous thrombosis) were assessed based on Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ). Reported major thromboembolic events included TTP recurrences. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
End point timeframe:	
From Baseline up to 36 months	

Notes:

[8] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: percentage of subjects				
number (not applicable)	37.9	8.2		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Major Thromboembolic Events Including Thrombotic Thrombocytopenic Purpura

End point title	Number of Major Thromboembolic Events Including Thrombotic Thrombocytopenic Purpura <sup>[9]</sup>
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End point description:

Major thromboembolic events (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep venous thrombosis) were assessed based on SMQ. Reported major thromboembolic events included TTP recurrences. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[9] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: major thromboembolic events	11	4		

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to First Major thromboembolic event

End point title	Time to First Major thromboembolic event <sup>[10]</sup>
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End point description:

Time to first major thromboembolic event was defined as the duration of time (in days) from Baseline up to first major thromboembolic event in LTS16371. Subjects without an event during LTS16371 were censored at the end of the study. Kaplan-Meier method was used for the analysis. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience an aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, '99999' was used as a space filler which indicates that median and 95% CI data were not calculated due to very few subjects with events.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[10] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: days				
median (confidence interval 95%)	99999 (845.00 to 99999)	99999 (99999 to 99999)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Cognitive Function: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Absolute Score at Baseline, 36 Months Follow-up Visit, and Change From Baseline in RBANS Total Score at 36 Months Follow-up Visit

End point title	Cognitive Function: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Absolute Score at Baseline, 36 Months Follow-up Visit, and Change From Baseline in RBANS Total Score at 36 Months Follow-up Visit <sup>[11]</sup>
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End point description:

The RBANS is a 30-minute comprehensive screening test with five individual domains (immediate memory, delayed memory, attention, language, and visuospatial ability) to examine the cognitive mental status of a subject. Scores from all individual domain were aggregated into a total score and thus RBANS total score ranged from 40 to 160, where higher scores reflected better performance. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, 36 Months follow-up visit

Notes:

[11] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	38		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 26, 38)	89.7 (± 20.3)	92.7 (± 14.9)		
At 36 Months (n = 12, 32)	98.0 (± 16.6)	96.5 (± 17.0)		
Change at 36 Months (n = 12, 32)	2.1 (± 8.7)	4.2 (± 8.9)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Health-Related Quality of Life (HRQoL): Change From Baseline in Headache Impact Test (HIT-6) Total Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life (HRQoL): Change From Baseline in Headache Impact Test (HIT-6) Total Scores at Month 12, 24, and 36 Follow-up Visits <sup>[12]</sup>
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End point description:

HIT-6 is an easy to administer assessment that was used as a clinical evaluation of the impact of headache on a subject's QoL in both clinical practice and clinical research. The questionnaire included 6 questions covering the 6 areas of functioning most impacted in headache sufferers including pain, role functioning (the ability to carry out usual activities), social functioning, vitality (energy/ fatigue), cognitive functioning, and psychological/emotional distress. Total HIT-6 scores (sum of all individual questions) ranged from 36 (best outcome) to 78 (worst outcome), where higher scores indicated worse condition. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[12] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	45.0 (± 10.0)	48.2 (± 9.9)		
Change at 12 Months (n = 20, 43)	0.9 (± 6.5)	0.1 (± 7.0)		
Change at 24 Months (n = 19, 45)	1.2 (± 8.2)	-0.6 (± 8.7)		
Change at 36 Months (n = 14, 43)	0.6 (± 7.9)	1.4 (± 7.5)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire (SF-36) Health Survey - Physical Functioning Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Physical functioning domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in physical functioning domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[13] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	68.3 (± 28.9)	74.1 (± 23.6)		
Change at 12 Months (n = 20, 46)	1.3 (± 16.8)	1.5 (± 24.1)		
Change at 24 Months (n = 20, 45)	-0.8 (± 18.2)	5.7 (± 19.3)		
Change at 36 Months (n = 15, 43)	5.7 (± 17.4)	6.2 (± 18.9)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Role Functioning/Physical Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Role Functioning/Physical Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[14]</sup>
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Role Functioning/Physical domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in role functioning/physical domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[14] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	60.1 (± 31.9)	65.9 (± 30.6)		
Change at 12 Months (n = 19, 46)	-5.3 (± 19.3)	7.7 (± 35.4)		
Change at 24 Months (n = 20, 45)	4.1 (± 24.1)	7.1 (± 28.0)		
Change at 36 Months (n = 15, 43)	5.8 (± 20.0)	3.6 (± 28.6)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Role Functioning/Emotional Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Role Functioning/Emotional Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[15]</sup>
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Role functioning/emotional domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in role functioning/emotional domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[15] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.



End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	75.3 (± 25.6)	75.0 (± 29.4)		
Change at 12 Months (n = 19, 46)	-13.2 (± 31.0)	1.6 (± 38.0)		
Change at 24 Months (n = 20, 45)	-1.3 (± 32.5)	0.9 (± 33.7)		
Change at 36 Month (n = 15, 43)	-4.4 (± 20.6)	-3.7 (± 29.6)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Energy/Fatigue Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Energy/Fatigue Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[16]</sup>
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Energy/fatigue domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in energy/fatigue domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[16] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	50.9 (± 21.2)	52.4 (± 20.9)		
Change at 12 Months (n = 20, 45)	-0.3 (± 18.3)	2.0 (± 20.7)		
Change at 24 Months (n = 20, 45)	5.9 (± 21.4)	0.6 (± 21.7)		
Change at 36 Months (n = 15, 43)	7.5 (± 21.3)	3.9 (± 18.7)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Emotional well-being Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Emotional well-being Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[17]</sup>
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Emotional well-being domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in emotional well-being domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[17] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	72.1 (± 18.3)	70.1 (± 20.7)		
Change at 12 Months (n = 20, 45)	-9.3 (± 18.2)	-2.5 (± 21.1)		
Change at 24 Months (n = 20, 45)	-3.3 (± 18.9)	-2.0 (± 21.3)		
Change at 36 Months (n = 15, 43)	-0.7 (± 14.6)	-1.5 (± 19.3)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Social Functioning Domain Scores at Month 12,

## 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Social Functioning Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[18]</sup>
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### End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Social functioning domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in social functioning domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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### End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

### Notes:

[18] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	74.6 (± 25.3)	74.0 (± 28.5)		
Change at 12 Months (n = 20, 46)	-10.6 (± 26.7)	1.6 (± 35.1)		
Change at 24 Months (n = 20, 45)	0.0 (± 27.5)	-0.8 (± 33.8)		
Change at 36 Months (n = 15, 43)	0.8 (± 18.0)	-2.6 (± 31.9)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Pain Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form questionnaire Health Survey - Pain Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[19]</sup>
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### End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Pain domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in pain domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[19] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	68.4 (± 31.7)	68.0 (± 23.5)		
Change at 12 Months (n = 20, 46)	-1.8 (± 30.4)	0.3 (± 33.6)		
Change at 24 Months (n = 20, 45)	-9.4 (± 32.5)	5.0 (± 24.9)		
Change at 36 Months (n = 15, 43)	-5.2 (± 21.5)	3.7 (± 25.6)		

## Statistical analyses

No statistical analyses for this end point

## Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form Questionnaire (SF-36) Health Survey - General Health Domain Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form Questionnaire (SF-36) Health Survey - General Health Domain Scores at Month 12, 24, and 36 Follow-up Visits <sup>[20]</sup>
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. General Health domain scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in general health domain score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[20] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	66.4 (± 18.5)	53.1 (± 19.3)		
Change at 12 Months (n = 20, 46)	-4.0 (± 19.8)	4.9 (± 19.0)		
Change at 24 Months (n = 20, 45)	-1.5 (± 17.9)	4.8 (± 20.9)		
Change at 36 Months (n = 15, 43)	-4.7 (± 11.1)	3.6 (± 17.3)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Health-Related Quality of Life: Change From Baseline in 36-Item Short Form Questionnaire (SF-36) Health Survey - Change in Health Status Scores at Month 12, 24, and 36 Follow-up Visits

End point title	Health-Related Quality of Life: Change From Baseline in 36-Item Short Form Questionnaire (SF-36) Health Survey - Change in Health Status Scores at Month 12, 24, and 36 Follow-up Visits <sup>[21]</sup>
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End point description:

The SF-36 consisted of 36 items that was summarised into 8 domains: physical functioning, social functioning, role functioning/physical, role functioning/emotional, emotional well-being, energy/fatigue, pain, general health and an additional single item covering change in health status. Change in health status scores ranged from 0 (worst value) to 100 (best value), with higher scores reflecting better health status. Change from baseline in change in health status score at months 12, 24, and 36 were reported in this endpoint. Analysis was performed on efficacy ITO population which included subjects who were enrolled in LTS16371 and did not experience aTTP recurrence in previous study ALX0681-C301 or prior to the beginning of LTS16371. Here, 'n' = subjects with available data for each specified category.

End point type	Primary
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End point timeframe:

Baseline, Month 12, 24, and 36 Follow-up visits

Notes:

[21] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	49		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 29, 49)	45.7 (± 31.4)	53.6 (± 34.2)		
Change at 12 Months (n = 20, 46)	30.0 (± 40.2)	20.1 (± 44.0)		
Change at 24 Months (n = 20, 45)	21.3 (± 36.5)	10.6 (± 39.0)		
Change at 36 Months (n = 15, 43)	16.7 (± 33.6)	4.7 (± 37.1)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Drug-Induced Treatment-emergent (TE) Antidrug Antibodies (ADA) Positive Response

End point title	Percentage of Subjects With Drug-Induced Treatment-emergent (TE) Antidrug Antibodies (ADA) Positive Response <sup>[22]</sup>
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End point description:

Drug-induced TE ADA positive was based on the outcome of a tiered assay approach that included a modified ADA (mADA) method to eliminate the effects of pre-existing antibodies (pre-Ab). TE ADA responses reported here included both pre-Ab positive and negative responses. A subject was considered as drug-induced TE ADA positive if post-dose samples were positive, regardless of the status of pre-dose samples in the ADA and modified ADA assay. Analysis was performed on overall ITO population which included subjects who were enrolled in LTS16371, grouped by whether they received caplacizumab during previous study ALX0681-C301 versus those who never received caplacizumab before enrollment in LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[22] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	75		
Units: percentage of subjects				
number (not applicable)	0	10.7		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) <sup>[23]</sup>
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End point description:

An AE was any untoward medical occurrence in a clinical study subject administered a medicinal product and which did not necessarily had to have a causal relationship with the treatment. An SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. Analysis was performed on overall ITO population which included subjects who were enrolled in LTS16371,

grouped by whether they received caplacizumab during previous study ALX0681-C301 versus those who never received caplacizumab before enrollment in LTS16371.

End point type	Primary
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End point timeframe:

From Baseline up to 36 months

Notes:

[23] - 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: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	75		
Units: subjects				
At least one AE	26	68		
At least one SAE	16	28		
At least one AE leading to death	1	0		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 36 months

Adverse event reporting additional description:

Analysis was performed on overall ITO population which included subjects who were enrolled in LTS16371, grouped by whether they received caplacizumab during previous study ALX0681-C301 versus those who never received caplacizumab before enrollment in LTS16371.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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### Reporting groups

Reporting group title	Standard of Care (Treated in Study C301)
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Reporting group description:

Subjects who completed study ALX0681-C301 with SoC (plasma exchange [PE], corticosteroid and other immunosuppressive agents) treatment were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to investigational medicinal product [IMP], withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg intravenous (IV) dose followed by a daily 10 milligrams (mg) subcutaneous (SC) injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Reporting group title	Caplacizumab (Treated in Study C301)
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Reporting group description:

Subjects who completed study ALX0681-C301 and received caplacizumab with PE and immunosuppressive agents were enrolled in study LTS16371. Subjects upon each recurrence of aTTP in LTS16371 and not meeting any criteria (namely: pregnancy, history of severe and/or serious hypersensitivity reaction to IMP, withdrawal before receiving IMP, received more than 1 PE) were treated with caplacizumab initial 10 mg IV dose followed by a daily 10 mg SC injections during the period of PE and for 30 days after stop of PE (and eventually 28-day extension period, if needed). Subjects with or without recurrence were followed up twice yearly up to maximum of 36 months in LTS16371.

Serious adverse events	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 29 (55.17%)	28 / 75 (37.33%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	



Invasive Ductal Breast Carcinoma alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 75 (1.33%) 0 / 1 0 / 0	
Plasma Cell Myeloma alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 75 (1.33%) 0 / 1 0 / 0	
Renal Cell Carcinoma alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 75 (0.00%) 0 / 0 0 / 0	
Transitional Cell Carcinoma alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 75 (0.00%) 0 / 0 0 / 0	
Surgical and medical procedures Abortion Induced alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	2 / 75 (2.67%) 0 / 2 0 / 0	
Cholecystectomy alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 75 (1.33%) 0 / 1 0 / 0	
Pregnancy, puerperium and perinatal conditions Abortion Spontaneous			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-Eclampsia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Colpocele			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterocele			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic Disorder			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
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			
Allergic Transfusion Reaction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage Intracranial			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic Thrombocytopenic Purpura			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	8 / 29 (27.59%)	11 / 75 (14.67%)	
occurrences causally related to treatment / all	0 / 9	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Gastrointestinal Haemorrhage			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis Membranous			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Urinary Tract			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Infarct			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 29 (6.90%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis Viral			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 29 (3.45%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Aseptic			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic Herpes Zoster			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	2 / 75 (2.67%) 0 / 3 0 / 0	
Pneumonia Pneumococcal alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 75 (1.33%) 0 / 1 0 / 0	
Upper Respiratory Tract Infection alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 75 (0.00%) 0 / 0 0 / 0	
Urinary Tract Infection alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 75 (1.33%) 0 / 1 0 / 0	

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

<b>Non-serious adverse events</b>	Standard of Care (Treated in Study C301)	Caplacizumab (Treated in Study C301)	
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 29 (75.86%)	58 / 75 (77.33%)	
Investigations Adamts13 Activity Decreased alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)  Blood Cholesterol Increased alternative dictionary used: MedDRA 22.0	0 / 29 (0.00%) 0	13 / 75 (17.33%) 13	

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	4 / 75 (5.33%) 4	
Injury, poisoning and procedural complications Contusion alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	2 / 75 (2.67%) 2	
Vascular disorders Hypertension alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	1 / 75 (1.33%) 1	
Nervous system disorders Dizziness alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)  Headache alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)  Paraesthesia alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)  Seizure alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2  9 / 29 (31.03%) 9  5 / 29 (17.24%) 5  2 / 29 (6.90%) 2	10 / 75 (13.33%) 10  16 / 75 (21.33%) 17  4 / 75 (5.33%) 4  1 / 75 (1.33%) 1	
General disorders and administration site conditions Asthenia alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)  Fatigue	2 / 29 (6.90%) 2	0 / 75 (0.00%) 0	



<p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 29 (3.45%)</p> <p>1</p> <p>3 / 29 (10.34%)</p> <p>3</p>	<p>7 / 75 (9.33%)</p> <p>7</p> <p>3 / 75 (4.00%)</p> <p>3</p>	
<p>Immune system disorders</p> <p>Drug Hypersensitivity</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypersensitivity</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p> <p>2 / 29 (6.90%)</p> <p>2</p>	<p>4 / 75 (5.33%)</p> <p>5</p> <p>1 / 75 (1.33%)</p> <p>1</p>	
<p>Gastrointestinal disorders</p> <p>Abdominal Pain</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal Pain Upper</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>alternative dictionary used: MedDRA 22.0</p>	<p>2 / 29 (6.90%)</p> <p>2</p> <p>3 / 29 (10.34%)</p> <p>3</p> <p>1 / 29 (3.45%)</p> <p>1</p> <p>5 / 29 (17.24%)</p> <p>5</p>	<p>3 / 75 (4.00%)</p> <p>3</p> <p>4 / 75 (5.33%)</p> <p>4</p> <p>5 / 75 (6.67%)</p> <p>5</p> <p>5 / 75 (6.67%)</p> <p>5</p>	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toothache</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 29 (3.45%)</p> <p>1</p> <p>2 / 29 (6.90%)</p> <p>2</p>	<p>7 / 75 (9.33%)</p> <p>7</p> <p>1 / 75 (1.33%)</p> <p>1</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 29 (10.34%)</p> <p>3</p>	<p>7 / 75 (9.33%)</p> <p>7</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Erythema</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p> <p>1 / 29 (3.45%)</p> <p>1</p> <p>0 / 29 (0.00%)</p> <p>0</p> <p>1 / 29 (3.45%)</p> <p>1</p>	<p>0 / 75 (0.00%)</p> <p>0</p> <p>6 / 75 (8.00%)</p> <p>7</p> <p>5 / 75 (6.67%)</p> <p>5</p> <p>4 / 75 (5.33%)</p> <p>4</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back Pain</p> <p>alternative dictionary used:</p>	<p>2 / 29 (6.90%)</p> <p>2</p>	<p>8 / 75 (10.67%)</p> <p>8</p>	

MedDRA 22.0			
subjects affected / exposed	2 / 29 (6.90%)	4 / 75 (5.33%)	
occurrences (all)	2	4	
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 29 (0.00%)	5 / 75 (6.67%)	
occurrences (all)	0	5	
Herpes Zoster			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 29 (6.90%)	2 / 75 (2.67%)	
occurrences (all)	2	2	
Influenza			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 29 (10.34%)	7 / 75 (9.33%)	
occurrences (all)	3	7	
Lower Respiratory Tract Infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 29 (6.90%)	4 / 75 (5.33%)	
occurrences (all)	2	4	
Nasopharyngitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 29 (20.69%)	6 / 75 (8.00%)	
occurrences (all)	6	6	
Rhinitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 29 (6.90%)	2 / 75 (2.67%)	
occurrences (all)	2	2	
Tonsillitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 29 (6.90%)	1 / 75 (1.33%)	
occurrences (all)	2	1	
Tooth Abscess			
alternative dictionary used: MedDRA 22.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p>	<p>0 / 75 (0.00%)</p> <p>0</p>	
<p>Upper Respiratory Tract Infection</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 29 (10.34%)</p> <p>3</p>	<p>7 / 75 (9.33%)</p> <p>7</p>	
<p>Urinary Tract Infection</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 29 (10.34%)</p> <p>3</p>	<p>4 / 75 (5.33%)</p> <p>5</p>	
<p>Metabolism and nutrition disorders</p> <p>Hypercholesterolaemia</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p>	<p>2 / 75 (2.67%)</p> <p>2</p>	
<p>Hypokalaemia</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p>	<p>2 / 75 (2.67%)</p> <p>2</p>	
<p>Iron Deficiency</p> <p>alternative dictionary used: MedDRA 22.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 29 (3.45%)</p> <p>1</p>	<p>5 / 75 (6.67%)</p> <p>5</p>	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported