Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants Who Have Thrombotic Microangiopathy Associated With a Trigger

Summary

EudraCT number	2020-005328-13
Trial protocol	NL BE IT
Global end of trial date	22 December 2022

Results information

Result version number	v1 (current)
This version publication date	04 January 2024
First version publication date	04 January 2024

Trial information

Trial identification

Sponsor protocol code	ALXN1210-TMA-315

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04743804
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, United States, 02210
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 147100615, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +33 147100615, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2022
Global end of trial reached?	Yes
Global end of trial date	22 December 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of ravulizumab in the treatment of participants with TMA

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	16
EEA total number of subjects	7

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)	0
Adults (18-64 years)	10
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was initiated on 27 Apr 2021. Enrollment in the study was halted on 06 Oct 2022. Participants already enrolled in the study continued to be dosed with study intervention and to perform study visits through 30 Dec 2022, LPLV actually took place on 22 Dec 2022.

Pre-assignment

Screening details:

Due to continued enrollment challenges, Alexion decided to terminate this study prematurely. There were no safety or efficacy concerns throughout the course of study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ravulizumab

Arm description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Arm title	Placebo

Arm description:

Participants received weight-based dosages of placebo matched to ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of placebo matched to ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo matched to ravulizumab at prespecifed time points.

Number of subjects in period 1	Ravulizumab	Placebo
Started	9	7
Received at least 1 dose of study drug	9	7
Completed	4	1
Not completed	5	6
Adverse event, serious fatal	3	-
Consent withdrawn by subject	-	1
Physician decision	-	1
Unspecified	1	-
Study Terminated by Sponsor	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Ravulizumab
Reporting group description:	
Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.	
Reporting group title	Placebo
Reporting group description:	
Participants received weight-based dosages of placebo matched to ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of placebo matched to ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.	

Reporting group values	Ravulizumab	Placebo	Total
Number of subjects	9	7	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	3	10
From 65-84 years	2	4	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	48.2	57.7	
standard deviation	± 15.75	± 17.70	-
Sex: Female, Male Units: participants			
Female	6	4	10
Male	3	3	6

End points

End points reporting groups

Reporting group title	Ravulizumab

Reporting group description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.

Reporting group title	Placebo

Reporting group description:

Participants received weight-based dosages of placebo matched to ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of placebo matched to ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.

Primary: Number of Participants With Complete Thrombotic Microangiopathy (TMA) Response at Week 26

End point title	Number of Participants With Complete Thrombotic Microangiopathy (TMA) Response at Week 26[1]

End point description:

TMA response required the following: 1) Normalization of platelet count without transfusion support during the prior 7 days. 2) Normalization of LDH. 3) Improvement in glomerular filtration rate (eGFR) of >= 30% compared to baseline. Participants must meet each TMA criterion at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. The Modified Intent-to-Treat Analysis Set included all randomized participants, excluding participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization.

End point type	Primary

End point timeframe:

Week 26

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: Due to early termination of study, no hypothesis testing for purpose of treatment comparisons was performed due to small sample size.

End point values	Ravulizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: participants	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete TMA Response

End point title	Time to Complete TMA Response

End point description:

The Kaplan-Meier estimate of time to event of complete TMA response is reported. TMA response required the following: 1) Normalization of platelet count without transfusion support during the prior 7 days. 2) Normalization of LDH. 3) Improvement in eGFR of >= 30% compared to baseline. Participants

must meet each TMA criterion at 2 separate assessments obtained at least 24 hours apart, and any measurement in between. Participants who did not have a response were censored at the date of last visit or study discontinuation at the time when the analysis was performed. The Modified Intent-to-Treat Analysis Set included all randomized participants, excluding participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization. 99999 signifies too few participants experienced the event to estimate the time to event median and upper limit of 95% CI.

End point type	Secondary

End point timeframe:

Baseline through Week 26

End point values	Ravulizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: days				
median (confidence interval 95%)	99999 (21.0 to 99999)	99999 (16.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants On Dialysis at Week 26

End point title	Number of Participants On Dialysis at Week 26

End point description:

The Modified Intent-to-Treat Analysis Set included all randomized participants, excluding participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization. Here, Number of Participants analyzed signifies those who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Week 26

End point values	Ravulizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Hematologic Response at Week 26

End point title	Number of Participants With Hematologic Response at Week 26

End point description:

Hematologic response required the following: (1) Normalization of platelet count without transfusion support during the prior 7 days, and (2) normalization of LDH. The Modified Intent-to-Treat Analysis Set included all randomized participants, excluding participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization.

End point type	Secondary

End point timeframe:

Week 26

End point values	Ravulizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: participants	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Renal Response at Week 26

End point title	Number of Participants With Renal Response at Week 26

End point description:

Renal response is improvement in eGFR of >= 30% compared to baseline. If a participant is on dialysis ≤5 days prior to the date of eGFR assessment, the eGFR will be set to 10 milliliter/minute/1.73 meter square (mL/min/1.73 m^2) for that assessment. If a participant is on dialysis during the entire 26 week randomized Treatment Period, or through early discontinuation of study drug, then the change in eGFR was not calculated. The Modified Intent-to-Treat Analysis Set included all randomized participants, excluding participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization.

End point type	Secondary

End point timeframe:

Week 26

End point values	Ravulizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: participants	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eGFR at Week 26

End point title	Change From Baseline in eGFR at Week 26

End point description:

If a participant is on dialysis during the entire 26 week randomized Treatment Period, or through early discontinuation of study drug, then the change in eGFR was not calculated. The Modified Intent-to-Treat Analysis Set included all randomized participants, excluding participants who enrolled prior to availability of ST-HUS and ADAMTS13 central laboratory results and were subsequently found to be ineligible after randomization. Here, Number of Participants analyzed signifies those who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Ravulizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: milliliter/minute/1.73 meter^2				
arithmetic mean (standard deviation)	25.8 (± 19.90)	17.5 (± 7.59)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 34

Adverse event reporting additional description:

The Safety Analysis Set included all participants who received at least 1 dose of study intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received weight-based dosages of placebo matched to ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of placebo matched to ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.

Reporting group title	Ravulizumab

Reporting group description:

Participants received weight-based dosages of ravulizumab for 26 weeks during the Initial Treatment Period. Participants received a loading dose of ravulizumab intravenously on Day 1, followed by maintenance dosing on Day 15 and once every 8 weeks thereafter.

Serious adverse events	Placebo	Ravulizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	6 / 9 (66.67%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Shunt thrombosis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombotic microangiopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (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			
Renal pseudoaneurysm			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Epstein-Barr viraemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Ravulizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer metastatic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metastases to bone			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Prostate cancer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	2 / 9 (22.22%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 9 (22.22%)	
occurrences (all)	5	2	
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Chills			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Device related thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Extravasation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Face oedema			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	6	0	
Illness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Penile dermatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pulmonary fibrosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	2 / 7 (28.57%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Psychiatric disorders			
Substance dependence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Delirium			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Transaminases increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Oxygen saturation decreased			

subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Facial bones fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Drain site complication			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Cardiac disorders			
Ventricular hypokinesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Stress cardiomyopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Left ventricular hypertrophy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Cardiac contractility decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Seizure			

subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Loss of consciousness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hydrocephalus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombotic microangiopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Bicytopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 9 (33.33%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	4 / 7 (57.14%)	2 / 9 (22.22%)	
occurrences (all)	10	2	
Abdominal discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	2 / 9 (22.22%)	
occurrences (all)	7	5	
Ileus paralytic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Faecaloma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pruritus allergic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Dermatitis diaper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hydronephrosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Euthyroid sick syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
SLE arthritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Joint instability			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 7 (42.86%)	2 / 9 (22.22%)	
occurrences (all)	3	2	
Device related infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Enterococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	3	
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Corynebacterium infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Vitamin D deficiency			
subjects affected / exposed	1 / 7 (14.29%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Dyslipidaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	2	2	
Hyperlipidaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hyperuricaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Steroid diabetes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Vitamin B12 deficiency subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 9 (11.11%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2021	The primary driver for this amendment was to allow for participants to be randomized based on local laboratory assessments (with the exception of the ST HUS screen and ADAMTS13 activity tests, which had to have been performed at the central laboratory) and allow for participants to be randomized prior to the availability of the ST-HUS screen and ADAMTS13 activity tests to align with current practice patterns for management of TMA participants. Additional changes were to update and clarify the TMA eligibility criteria, expand the window to assess eligibility for laboratory assessments to include ≤ 14 days prior to the Screening Period, define the estimands corresponding to the primary and key secondary endpoints according to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials, add additional endpoints to assess loss of TMA response, changes in hematological and renal response parameters, and survival, elevate changes in patient-reported outcomes as measured by FACIT-Fatigue to a secondary endpoint, update the efficacy analyses to be based on the modified Intent-to-Treat analysis set, and add COVID-19 risk assessment language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Planned interim analysis for sample size re-estimation and primary analysis as specified in PA2 were not conducted due to early termination of study. No hypothesis testing for purpose of treatment comparisons was performed due to small sample size.

Notes: