Clinical trial results:
A double-blind, randomized-withdrawal, placebo-controlled study to evaluate the efficacy and safety of human plasma-derived C1-esterase inhibitor as add-on to standard of care for the treatment of refractory antibody mediated rejection in adult renal transplant recipients

Summary

EudraCT number	2017-000348-17
Trial protocol	BE GB DE ES NL FR
Global end of trial date	20 January 2021

Results information

Result version number	v1 (current)
This version publication date	04 December 2021
First version publication date	04 December 2021

Trial information

Trial identification

Sponsor protocol code	CSL842_3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03221842
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring
Sponsor organisation address	1020 First Avenue, King of Prussia, United States, 19406
Public contact	Trial Registration Coordinator, CSL Behring LLC, +1 610-878-4000, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Coordinator, CSL Behring LLC, +1 610-878-4000, clinicaltrials@cslbehring.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	01 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 January 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of C1-INH in the treatment of refractory antibody mediated rejection (AMR) in renal allograft recipients.

Protection of trial subjects:

This study was carried out in accordance with the International Council for Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, and standard operating procedures for clinical research and development at CSL Behring.

Background therapy:

Background therapy is standard of care (IVIg with/without plasmapheresis).

Evidence for comparator: -

Actual start date of recruitment	06 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	63
EEA total number of subjects	39

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)	57
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Sponsor terminated the study for business reasons. Because of the study termination, there were limitations in interpreting analyses and efficacy results based on small numbers of subjects. No subject reached the 48-month follow-up endpoint.

Period 1

Period 1 title	Period 1 (up to 13 weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	C1-INH

Arm description:

C1-esterase inhibitor (CSL842)

C1-esterase inhibitor: C1-esterase inhibitor is a human plasma-derived lyophilised powder for reconstitution administered at a dose of 60 IU/kg

Arm type	Experimental
Investigational medicinal product name	C1-esterase inhibitor (C1-INH)
Investigational medicinal product code	
Other name	CSL842
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

C1-esterase inhibitor is a human plasma-derived lyophilised powder for reconstitution at a dose of 60 IU/kg

Number of subjects in period 1	C1-INH
Started	63
Completed	53
Not completed	10
Physician decision	2
Adverse event, non-fatal	4
Terminated by sponsor	1
Unknown	2
Lost to follow-up	1

Period 2

Period 2 title	Period 2 (up to 14-38 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	C1-INH

Arm description:

C1-esterase inhibitor (CSL842)

Arm type	Experimental
Investigational medicinal product name	C1-esterase inhibitor (C1-INH)
Investigational medicinal product code	
Other name	CSL842
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

C1-esterase inhibitor is a human plasma-derived lyophilised powder for reconstitution administered at a dose of 60 IU/kg

Arm title	Placebo

Arm description:

Excipients of C1-INH plus albumin

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Excipients of C1-INH plus albumin

Number of subjects in period 2[1]	C1-INH	Placebo
Started	7	6
Completed	6	5
Not completed	1	1
Adverse event, serious fatal	-	1
Lack of efficacy	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only 13 participants that completed Period 1 were eligible to continue to Period 2.

Baseline characteristics

Reporting groups

Reporting group title	Period 1 (up to 13 weeks)

Reporting group description: -

Reporting group values	Period 1 (up to 13 weeks)	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	57	57	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	43.3		
standard deviation	± 13.83	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	36	36	

End points

End points reporting groups

Reporting group title	C1-INH
Reporting group description:	
C1-esterase inhibitor (CSL842) C1-esterase inhibitor: C1-esterase inhibitor is a human plasma-derived lyophilised powder for reconstitution administered at a dose of 60 IU/kg	
Reporting group title	C1-INH
Reporting group description:	
C1-esterase inhibitor (CSL842)	
Reporting group title	Placebo
Reporting group description:	
Excipients of C1-INH plus albumin	

Primary: Number and percent of participants with loss-of-response at the end-of-Treatment Period 2 (TP2)

End point title	Number and percent of participants with loss-of-response at the end-of-Treatment Period 2 (TP2)[1]
End point description:	
Loss of response is defined as 1 of the following, whichever occurs first: • Decline in Estimated Glomerular Filtration Rate (eGFR), or • Allograft failure, or • Subject death by any cause.	
End point type	Primary
End point timeframe:	
Up to approximately 25 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were used for this endpoint.

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: participants				
number (not applicable)				
Number	2	2		
Percent	33.3	40.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percent of Participants With All-cause Allograft Failure During TP2

End point title	Number and percent of Participants With All-cause Allograft Failure During TP2

End point description:

Allograft failure is defined as 1 of the following:
• Allograft nephrectomy, institution of permanent dialysis, or return to the transplant waitlist for renal transplant, whichever occurs first, OR
• Subject death by any cause

End point type	Secondary

End point timeframe:

Up to 25 weeks

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: participants				
number (not applicable)				
Number	0	1		
Percent	0	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Estimated Glomerular Filtration Rate at End of Treatment Period 1(TP1)

End point title	Absolute Change From Baseline in Estimated Glomerular Filtration Rate at End of Treatment Period 1(TP1)

End point description:

End point type	Secondary

End point timeframe:

Baseline and 13 weeks

End point values	C1-INH			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: mL/min/1.73m*2				
median (full range (min-max))	-0.75 (-17.0 to 7.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Estimated Glomerular Filtration Rate at end of TP2

End point title	Absolute Change From Baseline in Estimated Glomerular Filtration Rate at end of TP2

End point description:

End point type	Secondary

End point timeframe:

Baseline and 38 weeks

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: Absolute Change From Baseline in Estimat				
arithmetic mean (standard deviation)	7.75 (± 8.454)	15.25 (± 10.444)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percent of responders at the end-of-TP1

End point title	Number and percent of responders at the end-of-TP1

End point description:

Responders were defined as subjects whose End-of-TP1 eGFR was ≥ 90% of baseline eGFR and ≥ 20 mL/min/1.73 m2.

End point type	Secondary

End point timeframe:

Up to 13 weeks

End point values	C1-INH			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: responders				
number (not applicable)				
Number	33			
Percent	52.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of participants with any adverse event (AE) assessed as related to investigational product

End point title	Percent of participants with any adverse event (AE) assessed as related to investigational product

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 42 weeks after the time of first investigational product administration

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	6		
Units: percentage of participants				
number (not applicable)	20.6	16.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean pre-dose C1-esterase inhibitor functional activity

End point title	Mean pre-dose C1-esterase inhibitor functional activity

End point description:

End point type	Secondary

End point timeframe:

Up to 13 weeks

End point values	C1-INH			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percent				
arithmetic mean (standard deviation)				
week 2 (n=14)	168.86 (± 64.059)			
week 11 (n=13)	179.32 (± 58.551)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) for C1-INH functional activity

End point title	Maximum plasma concentration (Cmax) for C1-INH functional activity

End point description:

End point type	Secondary

End point timeframe:

Up to 72 hours after dose

End point values	C1-INH			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent				
arithmetic mean (standard deviation)				
Day 10 (n=14)	270.39 (± 90.166)			
Day 77 (n=10)	204.41 (± 78.478)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration time curve (AUC0-t) for C1-INH functional activity

End point title	Area under the plasma concentration time curve (AUC0-t) for C1-INH functional activity

End point description:

End point type	Secondary

End point timeframe:

Up to 72 hours after dose

End point values	C1-INH			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: h*%				
arithmetic mean (standard deviation)				
Day 10 (n=10) Day 77 (n=9)	15229.84819 (± 4149.16754) 12742.20883 (± 4445.31881)			

Statistical analyses

No statistical analyses for this end point

Secondary: The rate of change of eGFR during TP2 as defined by the slope of the mean regression of eGFR over time in TP2

End point title	The rate of change of eGFR during TP2 as defined by the slope of the mean regression of eGFR over time in TP2

End point description:

End point type	Secondary

End point timeframe:

Screening and up to approximately 38 weeks

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: number				
number (not applicable)				

Notes:

[2] - Because of the study termination, limited efficacy results are presented in this report.

[3] - Because of the study termination, limited efficacy results are presented in this report.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to all-cause allograft failure through the Follow up Period

End point title	Time to all-cause allograft failure through the Follow up Period

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 208 weeks

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: hours				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - No subject completed the follow-up period.

[5] - Because of the study termination, limited efficacy results are presented in this report.

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects surviving through the Follow-up Period

End point title	Proportion of subjects surviving through the Follow-up Period

End point description:

End point type	Secondary

End point timeframe:

Up to approximately 208 weeks

End point values	C1-INH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: percent of subjects				
number (not applicable)				

Notes:

[6] - No subject completed the follow-up period.

[7] - Because of the study termination, limited efficacy results are presented in this report.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 42 weeks per participant	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	C1-INH (Period 1)
Reporting group description: C1-esterase inhibitor (CSL842) C1-esterase inhibitor: C1-esterase inhibitor is a human plasma-derived lyophilised powder for reconstitution administered at a dose of 60 IU/kg	
Reporting group title	C1-INH (Period 2)
Reporting group description: -	
Reporting group title	Placebo (Period 2)
Reporting group description: -	

Serious adverse events	C1-INH (Period 1)	C1-INH (Period 2)	Placebo (Period 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 63 (39.68%)	1 / 7 (14.29%)	3 / 6 (50.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unevaluable event			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Transplant rejection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 63 (4.76%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 63 (3.17%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perinephric collection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 63 (4.76%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rhinovirus infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection pseudomonas			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	C1-INH (Period 1)	C1-INH (Period 2)	Placebo (Period 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 63 (73.02%)	4 / 7 (57.14%)	5 / 6 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Refractory cytopenia with unilineage dysplasia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 63 (9.52%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	7	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 63 (6.35%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Discomfort			
subjects affected / exposed	0 / 63 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oedema			

subjects affected / exposed	8 / 63 (12.70%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	9	1	0
Pain			
subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	1
Pyrexia			
subjects affected / exposed	5 / 63 (7.94%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	4 / 63 (6.35%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Dyspnoea			
subjects affected / exposed	5 / 63 (7.94%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Epistaxis			
subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	10	0	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	18 / 63 (28.57%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	32	0	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 63 (12.70%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	9	0	0
Leukopenia			
subjects affected / exposed	5 / 63 (7.94%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	7	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 63 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Anal pruritus			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	11 / 63 (17.46%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	23	0	0
Nausea			
subjects affected / exposed	9 / 63 (14.29%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	12	0	1
Vomiting			
subjects affected / exposed	11 / 63 (17.46%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	13	0	0
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	5 / 63 (7.94%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Dermatitis papillaris capillitii			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	6 / 63 (9.52%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Focal segmental glomerulosclerosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Body tinea			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Conjunctivitis viral			
subjects affected / exposed	0 / 63 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cytomegalovirus infection			
subjects affected / exposed	3 / 63 (4.76%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Staphylococcal infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Trichomoniasis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	2 / 63 (3.17%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 63 (1.59%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	3 / 63 (4.76%)	1 / 7 (14.29%)	1 / 6 (16.67%)
occurrences (all)	3	1	1
Hyperphosphataemia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			

subjects affected / exposed	4 / 63 (6.35%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Metabolic acidosis			
subjects affected / exposed	5 / 63 (7.94%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	6	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2017	1. A Non-responder Follow-up Period is added for subjects who are non-responders after TP1. These subjects will be followed until graft failure or up to 48 months after enrollment. Statistical analyses are amended to reflect this change. 2. Pregnancy tests are added at monthly intervals. 3. Additional time points are added for C1-INH activity/antigen and collection of retention samples in TP1. 4. Exclusion criterion 3 is deleted. 5. Inclusion criterion 5 is amended. 6. Exclusion criterion 4a (previously 5a) amended to include HBV as part of the viral hepatitis criterion. 7. New exclusion criterion 5 includes a history of HIV as collected in medical history at Screening 8. The criteria used to determine frequency of blood draws for creatinine measurement is changed from an increase of 20% to 10% above the previous value in TP2.
23 January 2019	1. Plasmapheresis is no longer mandatory if DSA is ≥ 5000 MFI. 2. Dosing at Week 13 is clarified. 3. Mean corpuscular hemoglobin concentration and mean corpuscular volume are not required safety assessments. 4. Week 13 Visit is clarified
31 January 2020	1. The responder definition is revised. 2. Definition of loss of response is changed. 3. The primary endpoint is changed from time to loss of response to loss of response status (binary: yes/no). 4. The secondary endpoints are revised. 5. The number of planned subjects and sites are increased. 6. Development of recurrent or persistent AMR is added as an efficacy assessment. 7. Timing for collecting serum creatinine is amended. 8. Monitoring of kidney function is added during the Responder Follow-up Period. 9. Exploratory endpoints are amended. 10. Study design rationale is revised to support changes to the primary endpoint. 11. Inclusion criteria 5, 6, and 7 are amended. 12. Exclusion criterion 8 is amended. 13. Dosing of C1-INH and placebo based on body weight is clarified. 14. Measured eGFR timing is clarified. 15. The adverse event observation period is amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 March 2020	Study sites were notified that a global screening/enrollment hold would be implemented due to the COVID-19 pandemic.	29 May 2020

Notes:

Limitations and caveats

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

The Sponsor terminated the study due to feasibility of enrolment. Due to study termination, there were limitations in interpreting analyses and efficacy results based on small numbers of subjects. No subject reached the 48-month follow-up endpoint.

Notes: