



Clinical trial results:

A Randomized Double-Blind Placebo-Controlled Study to Evaluate the Efficacy and Safety of CINRYZE (C1 Esterase Inhibitor [Human]) for the Treatment of Acute Antibody-Mediated Rejection in Kidney Transplant Subjects

Summary

EudraCT number	2015-000726-11
Trial protocol	NL DE ES
Global end of trial date	31 May 2019

Results information

Result version number	v1 (current)
This version publication date	14 June 2020
First version publication date	14 June 2020

Trial information

Trial identification

Sponsor protocol code	SHP616-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02547220
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, 1 866-842-5335, ClinicalTransparency@takeda.com
Scientific contact	Study Director, Shire, 1 866-842-5335, ClinicalTransparency@takeda.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	31 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 May 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of CINRYZE administered with plasmapheresis, plasma exchange, or immune adsorption treatments and sucrose-free intravenous immunoglobulin (IVIg) for the treatment of acute antibody-mediated rejection (AMR) of renal allograft in kidney transplant recipients as measured by the proportion of subjects with new or worsening transplant glomerulopathy (TG) at 6 months after treatment initiation.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	39
EEA total number of subjects	10

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)	32
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 49 sites between 20 May 2016 (first subject first visit) and 31 May 2019 (last subject last visit).

Pre-assignment

Screening details:

A total of 39 subjects were randomized and received treatment.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received a total of seven doses, with an initial 100 milliliter (mL) intravenous (IV) infusion containing 5000 units of placebo (100 mL 0.9 percent [%] sodium chloride) on Day 1 followed by 2500 units of placebo (100 mL 0.9% sodium chloride) on Days 3, 5, 7, 9, 11, and 13.

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

Dosage and administration details:

Subjects received an initial 100 mL IV infusion containing 5000 units of placebo on Day 1 followed by 2500 units of placebo on Days 3, 5, 7, 9, 11, and 13.

Arm title	CINRYZE
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Arm description:

Subjects received a total of seven doses, with an initial 100 mL intravenous (IV) infusion containing 5000 units of CINRYZE on Day 1 followed by 2500 units of CINRYZE in 100 mL of IV infusion on Day 3, 5, 7, 9, 11, and 13.

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

Dosage and administration details:

Subjects received an initial 100 mL IV infusion containing 5000 units of CINRYZE on Day 1 followed by 2500 units of CINRYZE in 100 mL of IV infusion on Day 3, 5, 7, 9, 11, and 13.

Number of subjects in period 1	Placebo	CINRYZE
Started	19	20
Completed	0	0
Not completed	19	20
Consent withdrawn by subject	1	-
Study terminated by sponsor	18	20

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received a total of seven doses, with an initial 100 milliliter (mL) intravenous (IV) infusion containing 5000 units of placebo (100 mL 0.9 percent [%] sodium chloride) on Day 1 followed by 2500 units of placebo (100 mL 0.9% sodium chloride) on Days 3, 5, 7, 9, 11, and 13.	
Reporting group title	CINRYZE
Reporting group description:	
Subjects received a total of seven doses, with an initial 100 mL intravenous (IV) infusion containing 5000 units of CINRYZE on Day 1 followed by 2500 units of CINRYZE in 100 mL of IV infusion on Day 3, 5, 7, 9, 11, and 13.	

Reporting group values	Placebo	CINRYZE	Total
Number of subjects	19	20	39
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	51.9	49.2	
standard deviation	± 12.49	± 13.45	-
Gender categorical			
Units: Subjects			
Female	9	5	14
Male	10	15	25
Race/Ethnicity, Customized			
Units: Subjects			
White	12	13	25
American Indian or Alaska Native	0	0	0
Asian/Non-Japanese	5	1	6
Asian/Japanese	0	0	0
Native Hawaiian or Other Pacific Islander	0	2	2
Black or African American	2	2	4
Latino	0	1	1
Unknown	0	1	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	6	9
Not Hispanic or Latino	13	10	23
Unknown or Not Reported	3	4	7

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received a total of seven doses, with an initial 100 milliliter (mL) intravenous (IV) infusion containing 5000 units of placebo (100 mL 0.9 percent [%] sodium chloride) on Day 1 followed by 2500 units of placebo (100 mL 0.9% sodium chloride) on Days 3, 5, 7, 9, 11, and 13.	
Reporting group title	CINRYZE
Reporting group description: Subjects received a total of seven doses, with an initial 100 mL intravenous (IV) infusion containing 5000 units of CINRYZE on Day 1 followed by 2500 units of CINRYZE in 100 mL of IV infusion on Day 3, 5, 7, 9, 11, and 13.	

Primary: Percentage of Subjects With New or Worsening Transplant Glomerulopathy (TG) at Month 6 Post-Treatment

End point title	Percentage of Subjects With New or Worsening Transplant Glomerulopathy (TG) at Month 6 Post-Treatment
End point description: New or worsening TG at month 6 by the standard score was defined as an increase in one or more between qualifying biopsy and 6-month biopsy. New or worsening TG was measured by Banff 2013 criteria (standard score) using allograft glomerulopathy (Cg0-Cg3): Cg0- No GBM double contours by light microscopy (LM) or electron microscopy (EM); Cg1- no GBM double contours by LM but GBM double contours in at least 3 glomerular capillaries by EM; Cg2- Double contours affecting 26 to 50% of peripheral capillary loops in the most affected of nonsclerotic glomeruli; Cg3- Double contours affecting more than 50% of peripheral capillary loops in the most affected of nonsclerotic glomeruli with a score range of 0 (no allograft glomerulopathy) and 3 (severe glomerulopathy). Percentage of subjects with new or worsening TG at Month 6 post treatment was reported. Full analysis set (FAS) was analysed, which consisted of all subjects who had taken at least 1 dose of investigational product.	
End point type	Primary
End point timeframe: Month 6	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Percentage of subjects				
number (not applicable)	47.4	50.0		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v CINRYZE

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.6857
Method	Fisher exact
Parameter estimate	Difference in proportion
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.4
upper limit	34.5

Notes:

[1] - Difference in proportion was calculated by the difference in proportion of new or worsening TG at 6 months between CINRYZE and placebo

Secondary: Number of Subjects With All-Cause Graft Failure at Month 48

End point title	Number of Subjects With All-Cause Graft Failure at Month 48
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End point description:

Graft failure was determined as the presence of one or more of the following criteria: institution of permanent dialysis (defined as dialysis treatment more than [$>$] 30 days), current transplant nephrectomy, and/or a clinical determination of cessation of kidney graft function and estimated glomerular filtration rate (eGFR) less than or equal to (\leq) 15 milliliter (mL)/minute (min)/1.73 meter (m)². This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyze at Month 48. Hence, data for this endpoint was not collected as planned, analyzed and reported.

End point type	Secondary
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End point timeframe:

Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Subjects				

Notes:

[2] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[3] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Renal Function up to Month 48

End point title	Change From Baseline in Renal Function up to Month 48
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End point description:

Renal function was measured as glomerular filtration rate calculated by the modification of diet in renal disease (eGFRMDRD). This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
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End point timeframe:
Baseline, up to Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: milliliter per minute (mL/min)				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[5] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline With Pre-Antibody-Mediated Rejection (AMR) in Renal Function up to Month 48

End point title	Change From Baseline With Pre-Antibody-Mediated Rejection (AMR) in Renal Function up to Month 48
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End point description:

Renal function was measured as glomerular filtration rate calculated by the modification of diet in renal disease (eGFRMDRD). Pre-AMR baseline was the highest eGFRMDRD value obtained following the kidney transplant and within 30 days prior to the qualifying AMR episode. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
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End point timeframe:

Pre-AMR Baseline, up to Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[6]	0 ^[7]		
Units: mL/min				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[7] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Proteinuria Levels at Month 48

End point title	Number of Subjects With Proteinuria Levels at Month 48
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End point description:

Proteinuria included spot urine protein, urine creatinine, and urine protein/urine creatinine ratio. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to

analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
End point timeframe:	
Month 48	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: Subjects				

Notes:

[8] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[9] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Antibody-Mediated Rejection (AMR) Baseline in Histopathology per Banff Criteria at Month 6

End point title	Change From Pre-Antibody-Mediated Rejection (AMR) Baseline in Histopathology per Banff Criteria at Month 6
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End point description:

Histopathological diagnosis of acute rejection was measured by Banff 2013 criteria: Glomerulitis score (g0-g3), allograft glomerulopathy (Cg0-cg3), Tubulitis score (T0-T3), Intimal arteritis score (V0-V3), peritubular capillaritis (PTC) (ptc0-ptc3) and Interstitial Inflammation score (i0-i3). The histopathology was a composite of the sub-scores. Each of the sub-scores or histopathology score ranges from 0 (no histopathology) to 3 (more severe histopathology). This study was prematurely terminated at Month 36 due to futility issue. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
End point timeframe:	
Pre-AMR Baseline, Month 6	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[10]	0 ^[11]		
Units: milliliter				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[11] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With All-Cause Graft Failure at Month 6

End point title	Number of Subjects With All-Cause Graft Failure at Month 6
End point description:	
Graft failure was determined by the presence of one or more of the following criteria: institution of permanent dialysis (defined as dialysis treatment more than [$>$] 30 days), current transplant nephrectomy, and/or a clinical determination of cessation of kidney graft function and estimated glomerular filtration rate (eGFR) less than or equal to (\leq) 15 milliliter (mL)/minute (min)/1.73 meter (m) ² . This study was prematurely terminated at Month 36 due to futility issue. Hence, data for this endpoint was not collected as planned, analysed and reported.	
End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[12]	0 ^[13]		
Units: Subjects				

Notes:

[12] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[13] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Graft Failure due to Antibody-Mediated Rejection (AMR) Episodes at Month 48

End point title	Number of Subjects With Graft Failure due to Antibody-Mediated Rejection (AMR) Episodes at Month 48
End point description:	
Graft failure was determined by the presence of one or more of the following criteria: institution of permanent dialysis (defined as dialysis treatment more than [$>$] 30 days), current transplant nephrectomy, and/or a clinical determination of cessation of kidney graft function and estimated glomerular filtration rate (eGFR) less than or equal to (\leq) 15 milliliter (mL)/minute (min)/1.73 meter (m) ² . This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.	
End point type	Secondary
End point timeframe:	
Month 48	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[14]	0 ^[15]		
Units: Subjects				

Notes:

[14] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[15] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to All-Cause Graft Failure up to Month 48

End point title	Time to All-Cause Graft Failure up to Month 48
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End point description:

Graft failure was determined by the presence of one or more of the following criteria: institution of permanent dialysis (defined as dialysis treatment greater than [$>$] 30 days), current transplant nephrectomy, and/or a clinical determination of cessation of kidney graft function and estimated glomerular filtration rate (eGFR) less than or equal to (\leq) 15 milliliter (mL)/minute (min)/1.73 meter (m)². Time to all-cause graft failure in months was calculated as (Date of graft failure – Date of first dose + 1)/30.25. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[16]	0 ^[17]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[16] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[17] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Graft Failure due to Antibody-Mediated Rejection (AMR) Episodes up to Month 48

End point title	Time to Graft Failure due to Antibody-Mediated Rejection (AMR) Episodes up to Month 48
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End point description:

Graft failure was determined by the presence of one or more of the following criteria: institution of permanent dialysis (defined as dialysis treatment $>$ 30 days), current transplant nephrectomy, and/or a clinical determination of cessation of kidney graft function and eGFR \leq 15 mL/ min/1.73m². Time to graft failure due to AMR episodes in months was calculated as (Date of graft failure due to AMR – Date of first dose + 1)/30.25. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[18]	0 ^[19]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[18] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[19] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Resolution of the Qualifying Antibody-Mediated Rejection (AMR) Episodes at Month 48

End point title	Number of Subjects With Resolution of the Qualifying Antibody-Mediated Rejection (AMR) Episodes at Month 48
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End point description:

Number of subjects with resolution of the qualifying AMR episodes at Month 48. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
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End point timeframe:

Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[20]	0 ^[21]		
Units: Subjects				

Notes:

[20] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[21] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Qualifying Antibody-Mediated Rejection (AMR) Episodes up to Month 48

End point title	Time to Resolution of Qualifying Antibody-Mediated Rejection (AMR) Episodes up to Month 48
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End point description:

Time to resolution of qualifying AMR episodes was calculated as (Date of qualifying AMR resolution – Date of first dose + 1)/30.25. Subjects who didn't had resolution of qualifying AMR episodes and still on-study were censored at the date of last visit; Subjects who had completed the study without resolution of qualifying AMR were censored at the date of study completion; subjects who discontinued from the study without resolution of qualifying AMR were censored at the date of early discontinuation. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[22]	0 ^[23]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[22] - This study was prematurely terminated. Hence, data was not collected, analyzed for this end point.

[23] - This study was prematurely terminated. Hence, data was not collected, analyzed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Were Alive at Month 36

End point title	Number of Subjects Who Were Alive at Month 36
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End point description:

Number of subjects who were alive at Month 36 (study terminated instead of Month 48) were reported. Safety analysis set was analysed, which consisted of all subjects who had taken at least 1 dose of investigational product. This study was prematurely terminated at Month 36 due to futility issue. This outcome measure was planned to analyze at Month 48.

End point type	Secondary
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End point timeframe:

Month 36

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Subjects	19	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to All-Cause Mortality up to Month 48

End point title	Time to All-Cause Mortality up to Month 48
End point description: Time to all-cause mortality was calculated as (Date of discontinuation due to death – Date of first dose + 1)/30.25. Subjects who are alive and still on-study were censored at the date of last visit; Subjects who had completed the study were censored at the date of study completion; Subjects who discontinued from the study but not due to death were censored at the date of early discontinuation. This study was prematurely terminated at Month 36 due to futility issue. This endpoint was planned to analyse at Month 48. Hence, data for this endpoint was not collected as planned, analysed and reported.	
End point type	Secondary
End point timeframe: Up to Month 48	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[24]	0 ^[25]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[24] - This study was prematurely terminated. Hence, data was not collected, analysed for this end point.

[25] - This Study was prematurely terminated. Hence, data was not collected, analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)
End point description: An adverse event (AE) was any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurred in a subject participating in a clinical study with the sponsor's product, regardless of causal relationship. TEAEs were defined as events that started or worsened on or after the date of the first dose of investigational product, but no later than 30 days following the last dose of investigational product, within a treatment period. Safety analysis set was analysed, which consisted of all subjects who had taken at least 1 dose of investigational product.	
End point type	Secondary
End point timeframe: From start of study drug administration up to study termination (Month 36)	

End point values	Placebo	CINRYZE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: Subjects	16	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to study termination (Month 36)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received a total of seven doses with an initial 100 mL intravenous (IV) infusion containing 5000 units of placebo (100 mL 0.9% sodium chloride) on day 1 followed by 2500 units of placebo (100 mL 0.9% sodium chloride) on Days 3, 5, 7, 9, 11, and 13.

Reporting group title	CINRYZE
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Reporting group description:

Subjects received a total of seven doses with an initial 100 mL intravenous (IV) infusion containing 5000 units of CINRYZE on Day 1 followed by 2500 units of CINRYZE in 100 mL of IV infusion on Day 3, 5, 7, 9, 11, and 13.

Serious adverse events	Placebo	CINRYZE	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)	3 / 20 (15.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site thrombosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			

subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Klebsiella sepsis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	CINRYZE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)	16 / 20 (80.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 19 (10.53%)	1 / 20 (5.00%)	
occurrences (all)	3	2	
Lymphocele			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 19 (10.53%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nodule			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	2 / 19 (10.53%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Sinus disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood bicarbonate increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood magnesium decreased			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Blood potassium increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Blood urea increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Blood uric acid increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Haemoglobin decreased subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	0 / 20 (0.00%) 0	
Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Injury, poisoning and procedural complications			
Arteriovenous fistula site haematoma subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Citrate toxicity subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 5	
Complications of transplanted kidney			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Post procedural haemorrhage subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Toxicity to various agents subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Vascular access complication subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 3	0 / 20 (0.00%) 0	
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Tremor subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	0 / 20 (0.00%) 0	
Leukopenia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	2 / 20 (10.00%) 2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	2 / 19 (10.53%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	2 / 19 (10.53%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Dry mouth			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 19 (10.53%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Oesophagitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tooth disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rash pruritic			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Urticaria subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Proteinuria subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Muscle spasms subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Neck pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 20 (5.00%) 1	
Infections and infestations BK virus infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Catheter site infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Clostridium difficile colitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 20 (0.00%) 0	
Cytomegalovirus infection			

subjects affected / exposed	1 / 19 (5.26%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Peritonitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Urosepsis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 19 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Folate deficiency			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Metabolic acidosis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 20 (5.00%) 1	
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2015	Amendment:1 Added secondary objective ""To assess the overall subject survival status (proportion and time-to-event)" for consistency with endpoints and analyses". Removed the secondary objective/endpoint of frequency of AMR: "To assess the number of acute AMR episodes treated per protocol during the follow-up period".
25 June 2015	Amendment:2 Added an exploratory analysis to determine if early glomerular and/or endothelial pathology observed only on electron microscopy (cg score lesser than < 1b) affects long-term kidney graft survival.
01 September 2016	Amendment:3 Clarified that intravenous immunoglobulin (IVIg) is to be sucrose-free to avoid potential renal toxicity and dosed at no less than 100 mg/kg to allow more flexibility and adhere to site standard of care. Removed the limit for a maximum enrollment to add greater flexibility. Reorganized the secondary objectives into study entry to 6 months and study entry to 4 years to provide increased structure and clarity to the protocol. Added change in proteinuria as a secondary objective to better assess graft function. Added time to AMR resolution as a secondary objective to better assess CINRYZE effect. Revised the stratification for severity to specify estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease (eGFRMDRD) (ie, ≤ 15 mL/min/1.73 m ² or > 15 mL/min/1.73 m ²). Revised the definition of graft failure to specify that permanent dialysis is defined as dialysis treatment > 30 days, current transplant nephrectomy, or clinical determination of cessation of kidney graft (eGFRMDRD ≤ 15 mL/min/1.73 m ²). Clarified definitions of pre-AMR baseline and resolution of qualifying and recurrent AMR episodes. Revised the inclusion/exclusion criteria. Added criteria for adequate kidney function defined as having a pre-AMR baseline eGFRMDRD ≥ 20 mL/min/1.72 m ² if the qualifying AMR episode occurs ≤ 21 days after transplant or pre-AMR baseline eGFRMDRD ≥ 30 mL/min/1.72 m ² if the qualifying AMR episode occurs > 21 days after transplant. Revised the window for subject assessments from ± 14 days to ± 21 days for months 3 through 12 and to ± 28 days for months after Month 12 to allow greater flexibility to subjects and sites. Specified that Conmeds and AEs was collected through 30 days after the last dose of investigational product for each treatment period to ensure adequate information is collected for analysis of safety. Clarified the correct eGFRMDRD formula. Added in the 2013 updated criteria for Banff classification.
22 November 2017	Amendment:4 Retreatment of recurrent AMR episodes may occur "during the first 180 days after the qualifying biopsy for AMR," which was updated from "during the first 6 months of the study". To avoid confusion with the window of the Month 6 visit, the time to allow retreatment was set to 180 days. Serious adverse event procedure for thrombotic and thromboembolic events updated. Correction of typographical error: Units for eGFRMDRD value updated from milliliter per minute (mL/min)/1.72 square meter (m ²) to mL/min/1.73 m ² .

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.

This study was prematurely terminated at Month 36 due to futility issue.
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Notes: