



Clinical trial results:

A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group, Study to Investigate the Safety and Tolerability of Multiple Dose Administration of CSL112 in Subjects with Moderate Renal Impairment and Acute Myocardial Infarction

Summary

EudraCT number	2015-003017-26
Trial protocol	DE HU NL
Global end of trial date	19 June 2017

Results information

Result version number	v1 (current)
This version publication date	01 July 2018
First version publication date	01 July 2018

Trial information

Trial identification

Sponsor protocol code	CSL112_2001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02742103
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring LLC
Sponsor organisation address	1020 First Avenue, King of Prussia, United States, 19406
Public contact	Trial Registration Coordinator, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Coordinator, CSL Behring, 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	10 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the renal safety of CSL112 in subjects with moderate renal impairment and acute myocardial infarction after up to 4 weekly administrations of CSL112

Protection of trial subjects:

This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 2016
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	Israel: 10
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 28
Worldwide total number of subjects	83
EEA total number of subjects	54

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)	15

From 65 to 84 years	65
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

To ensure that at least 1/3 of the study population had an estimated glomerular filtration (eGFR) in the chronic kidney disease (CKD) Stage 3b range, no more than 2/3 of the study population were to have an eGFR in the CKD Stage 3a range. Randomization was stratified by eGFR and by medical history of diabetes.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CSL112

Arm description:

CSL112 (6 g) will be administered as a 2-hour intravenous (IV) infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total).

Arm type	Experimental
Investigational medicinal product name	CSL112
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

CSL112 contains apolipoprotein A-I (apoA-I), phosphatidylcholine (PC), cholate, and sucrose as a stabilizer. CSL112 (6 g) will be administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total).

Arm title	Placebo
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Arm description:

Placebo control (0.9% weight/volume sodium chloride solution, i.e., normal saline) administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total) in a volume matched to the CSL112 infusion.

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:

Placebo control (0.9% weight/volume sodium chloride solution, i.e., normal saline) administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total) in a volume matched to the CSL112 infusion.

Number of subjects in period 1	CSL112	Placebo
Started	55	28
Completed	46	23
Not completed	9	5
Adverse event, serious fatal	2	2
Consent withdrawn by subject	5	2
Moved to another town	-	1
Adverse event, non-fatal	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	CSL112
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Reporting group description:

CSL112 (6 g) will be administered as a 2-hour intravenous (IV) infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total).

Reporting group title	Placebo
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Reporting group description:

Placebo control (0.9% weight/volume sodium chloride solution, i.e., normal saline) administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total) in a volume matched to the CSL112 infusion.

Reporting group values	CSL112	Placebo	Total
Number of subjects	55	28	83
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)	11	4	15
From 65-84 years	42	23	65
85 years and over	2	1	3
Age continuous			
Units: years			
arithmetic mean	70.6	71.9	
standard deviation	± 10.95	± 10.12	-
Gender categorical			
Units: Subjects			
Female	18	10	28
Male	37	18	55

End points

End points reporting groups

Reporting group title	CSL112
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Reporting group description:

CSL112 (6 g) will be administered as a 2-hour intravenous (IV) infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total).

Reporting group title	Placebo
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Reporting group description:

Placebo control (0.9% weight/volume sodium chloride solution, i.e., normal saline) administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total) in a volume matched to the CSL112 infusion.

Subject analysis set title	Safety Population (SAF)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety (SAF) Population consisted of all subjects who received at least a partial dose of investigational product.

Subject analysis set title	Pharmacokinetic Population (PK)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All subjects in the SAF who had at least 1 measurable plasma concentration of either apoA-I or PC.

Primary: Percent of subjects with at least one occurrence of treatment-emergent renal Serious Adverse Events (SAEs) (SAF)

End point title	Percent of subjects with at least one occurrence of treatment-emergent renal Serious Adverse Events (SAEs) (SAF)
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End point description:

A renal SAE is defined as any SAE with a MedDRA preferred term included in the Acute Renal Failure narrow Standard MedDRA Query or a preferred term of renal tubular necrosis, renal cortical necrosis, renal necrosis, or renal papillary necrosis.

End point type	Primary
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End point timeframe:

Up to 9 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)	1.9	14.3		

Statistical analyses

Statistical analysis title	Rate difference between treatment groups
Comparison groups	CSL112 v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Method	Newcombe-Wilson
Parameter estimate	Rate difference (CSL112 - placebo)
Point estimate	-0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.296
upper limit	-0.005

Primary: Percent of subjects with treatment-emergent Acute Kidney Injury (AKI) (SAF)

End point title	Percent of subjects with treatment-emergent Acute Kidney Injury (AKI) (SAF)
End point description:	
Acute kidney injury is defined as an absolute increase in serum creatinine from baseline ≥ 0.3 mg/dL during the Active Treatment Period that is sustained upon repeat measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained, a single serum creatinine value that is increased from baseline ≥ 0.3 mg/dL (26.5 μ mol/L) during the Active Treatment Period would also fulfil the definition of AKI.	
End point type	Primary
End point timeframe:	
Up to 4 weeks	

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)	4.0	14.3		

Statistical analyses

Statistical analysis title	Rate difference between treatment groups
Comparison groups	CSL112 v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Method	Newcombe-Wilson
Parameter estimate	Rate difference (CSL112 - placebo)
Point estimate	-0.103

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.277
upper limit	0.025

Secondary: Number of subjects with any treatment-emergent adverse event (TEAE) (SAF)

End point title	Number of subjects with any treatment-emergent adverse event (TEAE) (SAF)
End point description:	
End point type	Secondary
End point timeframe:	
Up to 9 weeks	

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Number of subjects				
number (not applicable)	38	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of subjects with any TEAE (SAF)

End point title	Percent of subjects with any TEAE (SAF)
End point description:	
End point type	Secondary
End point timeframe:	
Up to 9 weeks	

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)	73.1	71.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of TEAEs (SAF)

End point title	Total number of TEAEs (SAF)
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End point description:

End point type	Secondary
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End point timeframe:

Up to 9 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Number				
number (not applicable)	111	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse drug reaction (ADR) or suspected ADR (SAF)

End point title	Number of subjects with treatment-emergent adverse drug reaction (ADR) or suspected ADR (SAF)
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End point description:

Adverse drug reactions or suspected adverse drug reactions are defined as:

- 1.All TEAEs, including local tolerability events, that begin during or within 1 hour after the end of an infusion; or
- 2.Those TEAEs that the investigator or sponsor indicate may be causally related to product administration; or
- 3.All TEAEs for which the Investigator's causality assessment is missing or indeterminate; or
- 4.All TEAEs for which the incidence in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more, provided the difference in incidence rates is 1% or more

End point type	Secondary
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End point timeframe:

Up to 9 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Number of subjects				
number (not applicable)	30	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with treatment-emergent ADR or suspected ADR (SAF)

End point title	Percentage of subjects with treatment-emergent ADR or suspected ADR (SAF)
End point description:	
End point type	Secondary
End point timeframe:	
Up to 9 weeks	

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)	57.7	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with change in renal status with central laboratory (SAF)

End point title	Number of subjects with change in renal status with central laboratory (SAF)
End point description:	
Changes in renal status defined as:	
◦Absolute increases from baseline in serum creatinine as follows:	
i. ≤ baseline value	
ii. > 0 to < 0.3 mg/dL	
iii. ≥ 0.3 to ≤ 0.5 mg/dL	
iv. > 0.5 mg/dL	
◦Increases in serum creatinine that are sustained for ≥ 24 hours upon repeat measurement that are greater than or equal to 1.5 x, 2 x, or 3.0 x the baseline value, or serum creatinine ≥ 4.0 mg/dL	
◦Decrease in eGFR ≥ 25% from baseline starting during the active treatment period and that is sustained at the final study visit	
End point type	Secondary

End point timeframe:

Baseline and up to 4 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Number of subjects				
number (not applicable)				
≤ baseline value	9	3		
> 0 to < 0.3 mg/dL	35	18		
≥ 0.3 to ≤ 0.5 mg/dL	4	4		
> 0.5 mg/dL	2	2		
≥ 1.5 × Baseline	1	0		
≥ 2 × Baseline	0	0		
≥ 3 × Baseline	0	0		
≥ 4.0 mg/dL	0	0		
Decrease in eGFR by ≥ 25%	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with change in renal status with central laboratory (SAF)

End point title	Percentage of subjects with change in renal status with central laboratory (SAF)
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End point description:

Changes in renal status defined as:

◦Absolute increases from baseline in serum creatinine as follows:

i. ≤ baseline value

ii. > 0 to < 0.3 mg/dL

iii. ≥ 0.3 to ≤ 0.5 mg/dL

iv. > 0.5 mg/dL

◦Increases in serum creatinine that are sustained for ≥ 24 hours upon repeat measurement that are greater than or equal to 1.5 x, 2 x, or 3.0 x the baseline value, or serum creatinine ≥ 4.0 mg/dL

◦Decrease in eGFR ≥ 25% from baseline starting during the active treatment period and that is sustained at the final study visit

End point type	Secondary
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End point timeframe:

Baseline and up to 4 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)				
≤ Baseline Value	17.3	10.7		
> 0 to < 0.3 mg/dL	67.3	64.3		
≥ 0.3 to ≤ 0.5 mg/dL	7.7	14.3		
> 0.5 mg/dL	3.8	7.1		
≥ 1.5 × Baseline	1.9	0		
≥ 2 × Baseline	0	0		
≥ 3 × Baseline	0	0		
≥ 4.0 mg/dL	0	0		
Decrease in eGFR by ≥ 25%	9.6	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with changes in hepatic status with central laboratory (SAF)

End point title	Number of subjects with changes in hepatic status with central laboratory (SAF)
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End point description:

Change from baseline in hepatic status and that is sustained for ≥ 24 hours upon repeat measurement defined as:

1. Alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN)
2. ALT > 5 x ULN
3. ALT > 10 x ULN
4. Serum total bilirubin > 1.5 x ULN
5. Serum total bilirubin > 2 x ULN

End point type	Secondary
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End point timeframe:

Baseline and up to 4 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Number of subjects				
number (not applicable)				
total bilirubin > 1.5 x ULN	4	1		
total bilirubin > 2 x ULN	1	0		
ALT > 3 x ULN	0	0		
ALT > 5 x ULN	0	0		
ALT > 10 x ULN	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of subjects with changes in hepatic status with central laboratory (SAF)

End point title	Percent of subjects with changes in hepatic status with central laboratory (SAF)
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End point description:

Change from baseline in hepatic status and that is sustained for ≥ 24 hours upon repeat measurement defined as:

1. ALT $> 3 \times$ upper limit of normal (ULN)

2. ALT $> 5 \times$ ULN

3. ALT $> 10 \times$ ULN

4. Serum total bilirubin $> 1.5 \times$ ULN

5. Serum total bilirubin $> 2 \times$ ULN

End point type	Secondary
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End point timeframe:

Baseline and up to 4 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)				
total bilirubin $> 1.5 \times$ ULN	7.7	3.7		
total bilirubin $> 2 \times$ ULN	1.9	0		
ALT $> 3 \times$ ULN	0	0		
ALT $> 5 \times$ ULN	0	0		
ALT $> 10 \times$ ULN	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent bleeding events (SAF)

End point title	Number of subjects with treatment-emergent bleeding events (SAF)
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End point description:

Bleeding events are as defined by the Bleeding Academic Research Consortium criteria (Mehran et al., 2011).

End point type	Secondary
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End point timeframe:

Up to 9 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Number of subjects				
number (not applicable)	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of subjects with treatment-emergent bleeding events (SAF)

End point title	Percent of subjects with treatment-emergent bleeding events (SAF)
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End point description:

End point type	Secondary
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End point timeframe:

Up to 9 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: Percent of subjects				
number (not applicable)	13.5	17.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with binding antibodies specific to apolipoprotein A-I (apo-A1) and CSL112 (SAF)

End point title	Percentage of subjects with binding antibodies specific to apolipoprotein A-I (apo-A1) and CSL112 (SAF)
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End point description:

End point type	Secondary
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End point timeframe:

Up to 9 weeks

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	22		
Units: Percent of subjects				
number (not applicable)				
CSL112 antibody	0	0		
apoA-I antibody	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma apoA-I and phosphatidylcholine (PC) accumulation ratio after infusion 4 (PK)

End point title	Plasma apoA-I and phosphatidylcholine (PC) accumulation ratio after infusion 4 (PK) ^[1]
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End point description:

End point type	Secondary
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End point timeframe:

Immediately after end of infusion

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Accumulation ratio is not calculated for subjects in the Placebo group.

End point values	CSL112			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: mg/dL				
arithmetic mean (standard deviation)				
apoA-I	1.2 (± 0.32)			
PC	1.0 (± 0.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline-corrected plasma concentration maximum (Cmax) after infusion 1 for apoA-I and PC (PK)

End point title	Baseline-corrected plasma concentration maximum (Cmax) after infusion 1 for apoA-I and PC (PK)
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End point description:

End point type	Secondary
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End point timeframe:

Immediately after end of infusion

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	28		
Units: mg/dL				
arithmetic mean (standard deviation)				
apoA-I	124.6 (± 25.38)	-4.5 (± 9.46)		
PC	198.4 (± 43.56)	-4.9 (± 15.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline-corrected plasma concentration maximum (Cmax) after infusion 4 for apoA-I and PC (PK)

End point title	Baseline-corrected plasma concentration maximum (Cmax) after infusion 4 for apoA-I and PC (PK)
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End point description:

End point type	Secondary
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End point timeframe:

Immediately after end of infusion

End point values	CSL112	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	21		
Units: mg/dL				
arithmetic mean (standard deviation)				
apoA-I	141.5 (± 41.11)	1.4 (± 23.57)		
PC	200.0 (± 71.78)	-13.2 (± 27.96)		

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

67 days for each subject

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	CSL112
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Reporting group description:

CSL112 (6 g) will be administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total).

Reporting group title	Placebo
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Reporting group description:

Placebo control (0.9% weight/volume sodium chloride solution, i.e., normal saline) administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (four infusions total) in a volume matched to the CSL112 infusion.

Serious adverse events	CSL112	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 52 (23.08%)	10 / 28 (35.71%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Injury, poisoning and procedural complications			
Post concussion syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	3 / 52 (5.77%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 52 (5.77%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 52 (1.92%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 52 (1.92%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 52 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			

Ataxia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 52 (1.92%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal erosion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 52 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	1 / 52 (1.92%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 28 (3.57%)	
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: 5 %

Non-serious adverse events	CSL112	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 52 (34.62%)	12 / 28 (42.86%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 52 (9.62%)	0 / 28 (0.00%)	
occurrences (all)	5	0	
Haemoglobin decreased			
subjects affected / exposed	3 / 52 (5.77%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 52 (9.62%)	1 / 28 (3.57%)	
occurrences (all)	5	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	5 / 52 (9.62%)	2 / 28 (7.14%)	
occurrences (all)	5	2	
Hypotension			
subjects affected / exposed	0 / 52 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
General disorders and administration			

site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 52 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 52 (7.69%)	1 / 28 (3.57%)	
occurrences (all)	4	1	
Nausea			
subjects affected / exposed	2 / 52 (3.85%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 52 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 52 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2016	-Revised the AKI definition -Added the evaluations that would be conducted for comparing AKI rates -Revised exclusion criterion 6 to clarify the definition of nephrotic range proteinuria at screening -Revised the secondary endpoints 2 and 3 regarding 1) the timing for capturing the occurrence of adverse drug reactions or suspected adverse drug reactions relative to investigational product infusion and 2) serum creatinine parameters -Revised the definition of study completion, to make the definition more conservative and easier to operationalize -Clarify the timing and number of repeat serum creatinine measurements for subsequent infusion eligibility -Defined "high grade proteinuria" on the locally performed urine dipstick at screening that would trigger the need for a central laboratory urinalysis assessment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported