Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomized, Multicenter, Proof of Concept and Dose-Finding Phase II Clinical Trial to Investigate the Safety, Tolerability and Efficacy of ADRECIZUMAB in Patients with Septic Shock and Elevated Adrenomedullin

Summary

EudraCT number	2016-003883-38
Trial protocol	DE BE NL
Global end of trial date	20 December 2019

Results information

Result version number	v1 (current)
This version publication date	03 January 2021
First version publication date	03 January 2021

Trial information

Trial identification

Sponsor protocol code	ADR-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03085758
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Adrenomed AG
Sponsor organisation address	Neuendorfstr. 15a, Hennigsdorf, Germany, 16761
Public contact	Clinical Development, Adrenomed AG, +49 33022056532, jzimmermann@adrenomed.com
Scientific contact	Clinical Development, Adrenomed AG, +49 33022056532, jzimmermann@adrenomed.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 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2019
Global end of trial reached?	Yes
Global end of trial date	20 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and tolerability of ADRECIZUMAB in patients with early septic shock and elevated bio-ADM (concentration of > 70 pg/ml) in treatment arm A (2 mg/kg) and in treatment arm B (4 mg/kg) over the 90 days study period.

Protection of trial subjects:

The study is approved by regulatory competent authorities and ethics committees in all participating countries. A Data and Safety Monitoring Board (DSMB) was established to review safety data from the trial. The DSMB received cases with a fatal outcome, reviewed cumulative mortality as well as serious adverse events (SAEs) and severe adverse events (AEs) data monthly.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 37
Country: Number of subjects enrolled	Belgium: 90
Country: Number of subjects enrolled	France: 124
Country: Number of subjects enrolled	Germany: 50
Worldwide total number of subjects	301
EEA total number of subjects	301

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)	98
From 65 to 84 years	173
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 08-Dec-2017 Last patient completed: 20-Dec-2019 Total study duration: 25 months

Pre-assignment

Screening details:

A total of 459 patients were enrolled for study participation. Of those, 301 patients were randomly assigned to receive Adrecizumab 2 mg/kg (72 patients), Adrecizumab 4 mg/kg (77 patients), and placebo (149 patients).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm A

Arm description:

Intravenous infusion over approximately 1 hour of single i.v. dose of 2 mg/kg Adrecizumab
Adrecizumab: Single i.v. dose of 2 mg/kg

Arm type	Experimental
Investigational medicinal product name	Adrecizumab
Investigational medicinal product code	HAM-8101
Other name	HAM-8101, enibarcimab
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single i.v. dose of 2 mg/kg

Arm title	Treatment Arm B

Arm description:

Intravenous infusion over approximately 1 hour of single i.v. dose of 4 mg/kg Adrecizumab
Adrecizumab: Single i.v. dose of 4 mg/kg

Arm type	Experimental
Investigational medicinal product name	HAM-8101
Investigational medicinal product code	Adrecizumab
Other name	HAM-8101, enibarcimab
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single i.v. dose of 4 mg/kg

Arm title	Control Group

Arm description:

Intravenous infusion over approximately 1 hour of single i.v. dose of Placebo of Adrecizumab
Placebo: Single i.v. dose of placebo

Arm type	Placebo

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

Dosage and administration details:

Single i.v. dose of placebo

Number of subjects in period 1	Treatment Arm A	Treatment Arm B	Control Group
Started	72	77	152
Completed	43	49	96
Not completed	29	28	56
Consent withdrawn by subject	2	2	1
Refusal to recall it up to day 90	-	-	1
Death	26	24	53
Pt seen by doctor in digestive surgery	-	1	-
Lost to follow-up	1	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Arm A
Reporting group description:	
Intravenous infusion over approximately 1 hour of single i.v. dose of 2 mg/kg Adrecizumab Adrecizumab: Single i.v. dose of 2 mg/kg	
Reporting group title	Treatment Arm B
Reporting group description:	
Intravenous infusion over approximately 1 hour of single i.v. dose of 4 mg/kg Adrecizumab Adrecizumab: Single i.v. dose of 4 mg/kg	
Reporting group title	Control Group
Reporting group description:	
Intravenous infusion over approximately 1 hour of single i.v. dose of Placebo of Adrecizumab Placebo: Single i.v. dose of placebo	

Reporting group values	Treatment Arm A	Treatment Arm B	Control Group
Number of subjects	72	77	152
Age categorical Units: Subjects			
Adults (18-64 years)	28	19	51
From 65-84 years	37	52	84
85 years and over	7	6	17
Age continuous Units: years			
arithmetic mean	66.2	68.8	69.3
full range (min-max)	30 to 94	18 to 89	21 to 94
Gender categorical Units: Subjects			
Female	27	24	66
Male	45	53	86
Location before ICU admission Units: Subjects			
Home	7	9	8
Hospital	65	68	144
Origin of Sepsis Units: Subjects			
Peritonitis	12	17	36
Lung	14	17	32
Urinary tract	18	10	26
Skin and soft tissue	2	8	14
Bile duct infection	4	5	6
Blood stream	4	5	6
Central nervous system	1	1	1
Catheter	0	0	4
Other	17	14	27
Body Mass Index (BMI)			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because height was not determined for one subject, therefore, no BMI was calculated. Treatment group C Row population differs from the Overall because height was not determined for one			

subject, therefore, no BMI was calculated.			
Units: kg/m2			
arithmetic mean	26.41	26.72	27.78
full range (min-max)	16.7 to 45.7	17.0 to 43.3	14.1 to 45.5
Body temperature			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because body temperature was not done for 6 subjects. Treatment group B Row population differs from the Overall because body temperature was not done for 4 subjects. Treatment group C Row population differs from the Overall because body temperature was not done for 7 subjects.			
Units: degrees C			
geometric mean	37.06	36.97	37.08
full range (min-max)	34.6 to 39.9	33.4 to 39.9	33.8 to 40.5
Heart rate			
Units: bpm			
geometric mean	104.38	97.40	96.37
full range (min-max)	51.0 to 158.0	60.0 to 151.0	44.0 to 153.0
Mean arterial pressure			
Units: mmHg			
arithmetic mean	73.18	71.35	72.49
full range (min-max)	43.0 to 99.0	32.0 to 104.0	22.0 to 110.0
Respiratory rate			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because respiratory rate was not done for 2 subjects Treatment group C Row population differs from the Overall because respiratory rate was not done for 3 subjects			
Units: breaths/min			
arithmetic mean	23.63	21.9	21.96
full range (min-max)	8.0 to 44.0	10.0 to 37.0	8.0 to 36.0
Bio-ADM			
Measure Description: bio-ADM measures the plasma level of the biological active Adrenomedullin, a vasoactive hormone that regulates blood pressure and vascular integrity Note results characterized as "3000" are to be read as >3000			
Units: pg/mL (local)			
arithmetic mean	284.30	305.15	755.92
full range (min-max)	74.9 to 1967.1	74.6 to 2328.9	74.3 to 3000
Blood lactate			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because blood lactate was not done for 4 subjects Treatment group B Row population differs from the Overall because blood lactate was not done for 2 subjects Treatment group C Row population differs from the Overall because blood lactate was not done for 3 subjects			
Units: mmol/L			
arithmetic mean	4.11	4.19	4.23
full range (min-max)	0.8 to 15.0	0.9 to 17.0	0.6 to 64.0
Creatinine			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because creatinine was not done for 1 subject Treatment group B Row population differs from the Overall because creatinine was not done for 1 subject			
Units: µmol/L			
arithmetic mean	189.649	199.891	192.801
full range (min-max)	31.82 to 582.00	53.04 to 834.50	32.10 to 912.29
Apache II Score			
Measure Description: Minimum score = 0; maximum score = 71. Increasing score is associated with increasing risk of hospital death. Measure Analysis Population Description: Treatment group A Row population differs from the Overall because Apache II Score was not done for 10 subjects Treatment group B Row population differs from			

the Overall because Apache II Score was not done for 11 subjects Treatment group C Row population differs from the Overall because Apache II Score was not done for 8 subjects			
Units: units on a scale			
arithmetic mean	31.4	31.8	31.5
full range (min-max)	17 to 42	20 to 42	14 to 53
Sequential Organ Failure Assessment (SOFA) Score			
Measure Description: The Sequential Organ Failure Assessment (SOFA) Score is a mortality prediction score that is based on the degree of dysfunction of six organ systems. Measure Analysis Population Description: Treatment group A Row population differs from the Overall because SOFA Score was not done for 11 subjects Treatment group B Row population differs from the Overall because SOFA Score was not done for 16 subjects Treatment group C Row population differs from the Overall because SOFA Score was not done for 20 subjects			
Units: units on a scale			
arithmetic mean	10.1	10.0	9.6
full range (min-max)	4 to 17	5 to 16	4 to 16

Reporting group values	Total		
Number of subjects	301		
Age categorical Units: Subjects			
Adults (18-64 years)	98		
From 65-84 years	173		
85 years and over	30		
Age continuous Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	117		
Male	184		
Location before ICU admission Units: Subjects			
Home	24		
Hospital	277		
Origin of Sepsis Units: Subjects			
Peritonitis	65		
Lung	63		
Urinary tract	54		
Skin and soft tissue	24		
Bile duct infection	15		
Blood stream	15		
Central nervous system	3		
Catheter	4		
Other	58		
Body Mass Index (BMI)			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because height was not determined for one subject, therefore, no BMI was calculated. Treatment group C Row population differs from the Overall because height was not determined for one subject, therefore, no BMI was calculated.			
Units: kg/m2			
arithmetic mean			

full range (min-max)	-		
Body temperature			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because body temperature was not done for 6 subjects. Treatment group B Row population differs from the Overall because body temperature was not done for 4 subjects. Treatment group C Row population differs from the Overall because body temperature was not done for 7 subjects.			
Units: degrees C geometric mean full range (min-max)	-		
Heart rate Units: bpm geometric mean full range (min-max)	-		
Mean arterial pressure Units: mmHg arithmetic mean full range (min-max)	-		
Respiratory rate			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because respiratory rate was not done for 2 subjects Treatment group C Row population differs from the Overall because respiratory rate was not done for 3 subjects			
Units: breaths/min arithmetic mean full range (min-max)	-		
Bio-ADM			
Measure Description: bio-ADM measures the plasma level of the biological active Adrenomedullin, a vasoactive hormone that regulates blood pressure and vascular integrity Note results characterized as "3000" are to be read as >3000			
Units: pg/mL (local) arithmetic mean full range (min-max)	-		
Blood lactate			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because blood lactate was not done for 4 subjects Treatment group B Row population differs from the Overall because blood lactate was not done for 2 subjects Treatment group C Row population differs from the Overall because blood lactate was not done for 3 subjects			
Units: mmol/L arithmetic mean full range (min-max)	-		
Creatinine			
Measure Analysis Population Description: Treatment group A Row population differs from the Overall because creatinine was not done for 1 subject Treatment group B Row population differs from the Overall because creatinine was not done for 1 subject			
Units: µmol/L arithmetic mean full range (min-max)	-		
Apache II Score			
Measure Description: Minimum score = 0; maximum score = 71. Increasing score is associated with increasing risk of hospital death. Measure Analysis Population Description: Treatment group A Row population differs from the Overall because Apache II Score was not done for 10 subjects Treatment group B Row population differs from the Overall because Apache II Score was not done for 11 subjects Treatment group C Row population differs from the Overall because Apache II Score was not done for 8 subjects			
Units: units on a scale			

arithmetic mean full range (min-max)	- 		
Sequential Organ Failure Assessment (SOFA) Score			
Measure Description: The Sequential Organ Failure Assessment (SOFA) Score is a mortality prediction score that is based on the degree of dysfunction of six organ systems. Measure Analysis Population Description: Treatment group A Row population differs from the Overall because SOFA Score was not done for 11 subjects Treatment group B Row population differs from the Overall because SOFA Score was not done for 16 subjects Treatment group C Row population differs from the Overall because SOFA Score was not done for 20 subjects			
Units: units on a scale arithmetic mean full range (min-max)	 -		

End points

End points reporting groups

Reporting group title	Treatment Arm A
Reporting group description:	
Intravenous infusion over approximately 1 hour of single i.v. dose of 2 mg/kg Adrecizumab Adrecizumab: Single i.v. dose of 2 mg/kg	
Reporting group title	Treatment Arm B
Reporting group description:	
Intravenous infusion over approximately 1 hour of single i.v. dose of 4 mg/kg Adrecizumab Adrecizumab: Single i.v. dose of 4 mg/kg	
Reporting group title	Control Group
Reporting group description:	
Intravenous infusion over approximately 1 hour of single i.v. dose of Placebo of Adrecizumab Placebo: Single i.v. dose of placebo	
Subject analysis set title	Adrecizumab Overall
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Treatment Arm A and Treatment Arm B combined	

Primary: Endpoints for Primary Objective (Safety and Tolerability of Adrecizumab: Mortality)

End point title	Endpoints for Primary Objective (Safety and Tolerability of Adrecizumab: Mortality)
End point description:	
The endpoints for the primary objective are to determine over the 90 days study period: Mortality related to ADRECIZUMAB	
End point type	Primary
End point timeframe:	
90 days	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: survival time				
geometric mean (standard error)	63.1453 (± 4.0940)	63.1578 (± 3.5967)	63.9809 (± 2.9466)	64.5744 (± 2.7582)

Statistical analyses

Statistical analysis title	Kaplan-Meier plot for the 90-day follow-up
Statistical analysis description:	
All-cause mortality for 90-day follow-up was evaluated using Kaplan-Meier plots comparing Adrecizumab (doses combined) vs. Placebo, and Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo (each with log-rank test without adjustment).	
Comparison groups	Control Group v Adrecizumab Overall

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7659
Method	Logrank

Primary: Endpoints for Primary Objective (Safety and Tolerability of Adrecizumab: Interruption of Infusion)

End point title	Endpoints for Primary Objective (Safety and Tolerability of Adrecizumab: Interruption of Infusion)[1]

End point description:

The endpoints for the primary objective are to determine over the 90 days study period:
Interruption of infusion due to intolerability of Adrecizumab

End point type	Primary

End point timeframe:

90 days

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: For only 1 patient, the infusion was interrupted and stopped prematurely.
This patient belonged to the Adrecizumab 4 mg/kg group.

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: Interruptions	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Primary: Endpoints for Primary Objective (Safety and Tolerability of Adrecizumab: Severity and Frequency of TEAEs)

End point title	Endpoints for Primary Objective (Safety and Tolerability of Adrecizumab: Severity and Frequency of TEAEs)[2]

End point description:

The endpoints for the primary objective are to determine over the 90 days study period:
Changes in severity and frequency of treatment-emergent adverse events

End point type	Primary

End point timeframe:

90 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In the Adrecizumab 2 mg/kg group, TEAEs were mild in 39 patients (54.2%), moderate in 54 patients (75.0%), and severe in 51 patients (70.8%; Table 14.2.1.3-1). In the Adrecizumab 4 mg/kg group, TEAEs were mild in 46 patients (59.7%), moderate in 60 patients (77.9%), and severe in 54 patients (70.1%). In the Placebo group, TEAEs were mild in 82 patients (53.9%), moderate in 109 patients (71.7%), and severe in 108 patients (71.1%).

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: Participants	68	74	142	142

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy to be Determined by Sepsis Support Index (SSI)

End point title	Efficacy to be Determined by Sepsis Support Index (SSI)

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	71	75	151	146
Units: score on a scale				
arithmetic mean (standard deviation)	8.4 (± 5.16)	9.1 (± 5.20)	8.1 (± 5.41)	8.8 (± 5.16)

Statistical analyses

No statistical analyses for this end point

Secondary: Sepsis Support Index (SSI)

End point title	Sepsis Support Index (SSI)

End point description:

Sepsis Support Index (SSI) at 28 day follow-up Minimum value possible is 0, maximum value is 14. A higher score means a worse outcome.

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	75	151	145
Units: score on a scale				
arithmetic mean (standard deviation)	13.3 (± 10.91)	14.6 (± 10.76)	12.8 (± 11.14)	14.0 (± 10.82)

Statistical analyses

No statistical analyses for this end point

Secondary: Penalized Sepsis Support Index (pSSI) at 14 Day Follow-up

End point title	Penalized Sepsis Support Index (pSSI) at 14 Day Follow-up

End point description:

Penalized Sepsis Support Index (pSSI) at day 14, defined similar to the SSI with the exception that patients that die get penalized by assigning the maximum value, i.e. the pSSI is set to 14 or 28, respectively. Minimum value possible is 0, maximum value is 14. A higher score means a worse outcome.

End point type	Secondary

End point timeframe:

day 14

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	71	75	151	146
Units: score on a scale				
arithmetic mean (standard deviation)	8.5 (± 5.26)	9.1 (± 5.20)	8.1 (± 5.42)	8.8 (± 5.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Persistent Organ Dysfunction or Death at 14 and 28 Day Follow-up

End point title	Persistent Organ Dysfunction or Death at 14 and 28 Day Follow-up

End point description:

Persistent organ dysfunction or death at 14 and 28 day follow-up

End point type	Secondary

End point timeframe:

day 14 and day 28

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: Count of participants				
Day 14	29	37	63	66
Day 28	25	25	49	50

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality Rate

End point title	Mortality Rate
End point description:	
Day 28 mortality rate	
End point type	Secondary
End point timeframe:	
Day 28	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: survival time				
arithmetic mean (standard error)	20.3484 (± 0.8694)	17.5630 (± 0.6592)	22.8783 (± 0.7627)	20.5162 (± 0.5903)

Statistical analyses

No statistical analyses for this end point

Secondary: SSI and pSSI Excluding the Renal Component

End point title	SSI and pSSI Excluding the Renal Component
End point description:	
Sepsis Support Index (SSI) and penalized Sepsis Support Index (pSSI) excluding the renal component. pSSI defined similar to the SSI with the exception that patients that die get penalized by assigning the maximum value, i.e. the pSSI is set to 14. Minimum value possible is 0, maximum value is 14. A higher score means a worse outcome.	
End point type	Secondary
End point timeframe:	
Day 14 and day 28	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	75	152	146
Units: score on a scale				
arithmetic mean (standard deviation)				
SSI Day 14	8.0 (± 5.21)	9.0 (± 5.24)	7.9 (± 5.42)	8.5 (± 5.24)
SSI Day 28	12.9 (± 11.03)	14.3 (± 10.80)	12.6 (± 11.17)	13.6 (± 10.90)
pSSI Day 14	8.1 (± 5.32)	9.0 (± 5.24)	7.9 (± 5.43)	8.6 (± 5.28)
pSSI Day 28	13.4 (± 11.47)	14.5 (± 10.92)	12.9 (± 11.30)	14.0 (± 11.17)

Statistical analyses

No statistical analyses for this end point

Secondary: SSI Weighted for Mortality

End point title	SSI Weighted for Mortality

End point description:

Sepsis Support Index (SSI) Weighted for Mortality. Minimum value possible is 0, maximum value is 14. A higher score means a worse outcome.

End point type	Secondary

End point timeframe:

Day 14

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	71	75	150	146
Units: score on a scale				
arithmetic mean (standard deviation)	10.2 (± 7.76)	10.7 (± 7.65)	9.9 (± 8.41)	10.5 (± 7.68)

Statistical analyses

No statistical analyses for this end point

Secondary: Sequential Organ Failure Assessment (SOFA) Score : Composite Measure: SOFA Score and Its Changes Over Time

End point title	Sequential Organ Failure Assessment (SOFA) Score : Composite Measure: SOFA Score and Its Changes Over Time

End point description:

Sequential Organ Failure Assessment (SOFA) Score: SOFA score change at Day 3 - baseline, delta = difference between maximum and minimum score during ICU stay, mean/maximum/total daily score during ICU stay, SOFA-3 (score limited to cardiovascular, respiratory and renal function).
SOFA score: Minimum possible score is 0, maximum is 24. A higher score meas a worse outcome. SOFA-3 score: Minimum possible score is 0, maximum is 12. A higher score meas a worse outcome.

End point type	Secondary

End point timeframe:
28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72[3]	77[4]	152[5]	149[6]
Units: score on a scale				
arithmetic mean (standard deviation)				
a) SOFA change	-0.9 (± 4.77)	-0.2 (± 4.87)	0.3 (± 5.33)	-0.5 (± 4.87)
b) SOFA delta score	4.2 (± 2.50)	4.8 (± 3.80)	3.8 (± 3.16)	4.5 (± 3.24)
c) SOFA maximum score	10.2 (± 3.77)	10.8 (± 4.46)	9.7 (± 3.94)	10.5 (± 4.13)
d) SOFA mean score	7.957 (± 3.7546)	8.319 (± 3.8129)	7.644 (± 3.5105)	8.143 (± 3.7751)
e) SOFA total score	38.9 (± 33.69)	54.9 (± 55.56)	44.1 (± 48.59)	47.1 (± 46.78)
f) SOFA-3 change	-1.7 (± 2.77)	-0.9 (± 2.81)	-0.9 (± 2.92)	-1.3 (± 2.80)
g) SOFA-3 delta score	3.5 (± 1.96)	3.5 (± 2.26)	3.1 (± 2.50)	3.5 (± 2.11)
h) SOFA-3 maximum score	7.2 (± 2.14)	7.2 (± 2.60)	6.8 (± 2.61)	7.2 (± 2.38)
i) SOFA-3 mean score	8.909 (± 6.5681)	9.336 (± 7.2622)	8.311 (± 8.0551)	9.129 (± 6.9118)
j) SOFA-3 total score	44.2 (± 42.36)	56.4 (± 51.13)	44.3 (± 46.45)	50.6 (± 47.40)

Notes:
[3] - Number of subjects analysed: a: 56; b, c, d, e, g, h, i, j:66; f:64
[4] - Number of subjects analysed: a: 56; b, c, d, e, g, h, i: 70; f: 68; j: 63
[5] - Number of subjects analysed: a: 116; b, c, d, e, g, h, i, j:137; f: 152; j, 139
[6] - Number of subjects analysed: a: 112; b, c, d, e, g, h, i: 136 ; f: 132; j: 139

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in Renal Function

End point title	Improvement in Renal Function
End point description:	
Improvement in renal function as change in penKid and creatinine (day 3 - day 1, day 7- day 1)	
End point type	Secondary
End point timeframe:	
Day 1, day 3 and day 7	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	75	151	145[7]
Units: Creatinine [µmol/L]; PenKid [pmol/L]				
arithmetic mean (standard deviation)				
Creatinine change baseline to day 3	-27.9 (± 85.65)	-11.7 (± 77.99)	-25.6 (± 109.12)	-27.9 (± 85.65)

Creatinine change baseline to day 7	-46.6 (± 140.38)	-44.9 (± 98.44)	-50.5 (± 125.35)	-45.7 (± 120.10)
PenKid change baseline to day 3	-28.3 (± 57.25)	-21.4 (± 59.07)	-34.8 (± 63.91)	-24.8 (± 58.10)
PenKid change baseline to day 7	-19.5 (± 83.88)	-19.7 (± 70.80)	-29.8 (± 83.27)	-19.6 (± 77.11)

Notes:

[7] - PenKid change baseline to day 7: 143 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stay at ICU/ Hospital

End point title	Duration of Stay at ICU/ Hospital

End point description:

Duration of stay at ICU / hospital

End point type	Secondary

End point timeframe:

90 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72[8]	77[9]	152[10]	149[11]
Units: Days				
arithmetic mean (standard deviation)				
Duration of hospital stay	12.3 (± 11.87)	13.4 (± 7.71)	11.2 (± 7.72)	12.8 (± 10.2)
Duration of ICU stay	9.6 (± 6.27)	11.0 (± 7.26)	9.3 (± 7.23)	10.3 (± 6.77)

Notes:

[8] - Subjects analyzed duration of hospital stay: 44
Subjects analysed duration of ICU stay: 49

[9] - Subjects analyzed duration of hospital stay: 42
Subjects analysed duration of ICU stay: 47

[10] - Subjects analyzed duration of hospital stay: 95
Subjects analysed duration of ICU stay: 99

[11] - Subjects analyzed duration of hospital stay: 86
Subjects analysed duration of ICU stay: 149

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Mean Arterial Pressure During Stay at ICU

End point title	Changes of Functional Parameter Mean Arterial Pressure During Stay at ICU

End point description:

Changes of Mean Arterial Pressure (MAP)

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: mmHg				
arithmetic mean (standard deviation)				
Change from baseline (minimum)	-7.2 (± 21.36)	-6.2 (± 18.44)	-6.4 (± 23.52)	-6.7 (± 19.84)
Change from baseline (maximum)	18.9 (± 23.54)	17.9 (± 19.73)	20.2 (± 21.26)	18.4 (± 21.64)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Creatinine During Stay at ICU

End point title	Changes of Functional Parameter Creatinine During Stay at ICU
End point description: Changes of creatinine	
End point type	Secondary
End point timeframe: 28 days	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	71[12]	76[13]	152[14]	147[15]
Units: µmol/L				
arithmetic mean (standard deviation)				
Baseline	189.649 (± 116.1689)	199.891 (± 130.9752)	192.801 (± 131.6193)	194.944 (± 123.7293)
Day 28	84.217 (± 88.1051)	79.488 (± 65.9763)	153.072 (± 120.3464)	81.380 (± 73.3867)

Notes:

[12] - 8 subjects analysed at day 28

[13] - 12 subjects analysed at day 28

[14] - 14 subjects analysed at day 28

[15] - 20 subjects analysed at day 28

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Partial Pressure of Oxygen in Arterial Blood(PaO2) / Fraction of Inspired Oxygen (FiO2) During Stay at ICU

End point title	Changes of Functional Parameter Partial Pressure of Oxygen in

	Arterial Blood(PaO2) / Fraction of Inspired Oxygen (FiO2) During Stay at ICU
End point description:	
Changes of Partial Pressure of Oxygen in Arterial Blood (PaO2) / Fraction of inspired oxygen (FiO2)	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	65	68	136	133
Units: mmHg				
arithmetic mean (standard deviation)	39.83 (± 155.237)	63.80 (± 156.771)	15.91 (± 164.238)	52.08 (± 155.896)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Blood Lactate During Stay at ICU

End point title	Changes of Functional Parameter Blood Lactate During Stay at ICU
End point description:	
Changes of blood lactate	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	66	70	144	136
Units: mmol/L				
arithmetic mean (standard deviation)	-1.94 (± 3.133)	-1.54 (± 5.247)	-1.49 (± 7.158)	-1.74 (± 4.340)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Fluid Balance During Stay at ICU

End point title	Changes of Functional Parameter Fluid Balance During Stay at ICU

End point description:

Changes of fluid balance - Last Observed Value Fluid balance low = </=1000 mL, high = >1000 mL

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	58[16]	65[17]	123[18]	123[19]
Units: percentage of participants				
number (not applicable)				
Low, ≤ 1000 mL	80.6	84.4	80.9	82.6
High, > 1000 mL	19.4	15.6	18.4	17.4

Notes:

[16] - Low, 58 subjects: High, 14 subjects

[17] - Low, 65 subjects; High, 12 subjects

[18] - Low, 123 subjects; High, 28 subjects

[19] - Low, 123 subjects
High, 26 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Mid-Regional Pro-Adrenomedullin (MR-proADM) During Stay at ICU

End point title	Changes of Functional Parameter Mid-Regional Pro-Adrenomedullin (MR-proADM) During Stay at ICU

End point description:

Changes of MR-proADM

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	61	63	127	124
Units: mmol/L				
arithmetic mean (standard deviation)	-5.029 (± 5.2829)	-4.608 (± 4.9512)	-4.030 (± 5.2887)	-4.815 (± 5.1006)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Inflammatory Marker Procalcitonine (PCT) During Stay at ICU

End point title	Changes of Functional Parameter Inflammatory Marker Procalcitonine (PCT) During Stay at ICU

End point description:

Changes of inflammatory marker Procalcitonine (PCT)

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	62	66	128	128
Units: ng/mL				
arithmetic mean (standard deviation)	-41.402 (± 125.0852)	-52.661 (± 78.1064)	-37.219 (± 78.3425)	-47.208 (± 103.2929)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Inflammatory Marker Interleukin-6 (IL-6) During Stay at ICU

End point title	Changes of Functional Parameter Inflammatory Marker Interleukin-6 (IL-6) During Stay at ICU

End point description:

Changes of inflammatory marker Interleukin-6 (IL-6)

End point type	Secondary

End point timeframe:

20 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	62	66	128	128
Units: pg/mL				
arithmetic mean (standard deviation)	-27648.3 (± 72859.19)	-37780.4 (± 119945.41)	-26236.2 (± 70315.50)	-32872.7 (± 99694.28)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes of Functional Parameter Dipeptidyl Peptidase 3 (DPP3) During Stay at ICU

End point title	Changes of Functional Parameter Dipeptidyl Peptidase 3 (DPP3) During Stay at ICU

End point description:

Changes of dipeptidyl peptidase 3 (DPP3)

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	62	66	128	128
Units: ng/mL				
arithmetic mean (standard deviation)	-11.56 (± 53.030)	-12.47 (± 42.270)	-9.38 (± 122.031)	-12.03 (± 47.596)

Statistical analyses

No statistical analyses for this end point

Secondary: Vasopressor Use (Adrenergic and Dopaminergic Agents, Highest Dose)

End point title	Vasopressor Use (Adrenergic and Dopaminergic Agents, Highest Dose)

End point description:

Vasopressor use (adrenergic and dopaminergic agents, highest dose)

End point type	Secondary

End point timeframe:

28 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: µg/kg/min				
arithmetic mean (standard deviation)	3.1414 (± 7.89069)	1.7307 (± 2.03233)	1.8276 (± 4.86110)	2.4124 (± 5.70006)

Statistical analyses

No statistical analyses for this end point

Secondary: Vasopressor Use (Adrenergic and Dopaminergic Agents, Lowest Dose)

End point title	Vasopressor Use (Adrenergic and Dopaminergic Agents, Lowest Dose)
End point description:	
Vasopressor use (adrenergic and dopaminergic agents, lowest dose)	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	77	152	149
Units: µg/kg/min				
arithmetic mean (standard deviation)	0.0570 (± 0.15449)	0.0358 (± 0.05762)	0.0528 (± 0.09866)	0.0461 (± 0.11518)

Statistical analyses

No statistical analyses for this end point

Secondary: Vasopressor Use (Adrenergic and Dopaminergic Agents, Duration)

End point title	Vasopressor Use (Adrenergic and Dopaminergic Agents, Duration)
End point description:	
Vasopressor use (adrenergic and Dopaminergic Agents, Lowest Dose)	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	68	77	150	145
Units: days				
arithmetic mean (standard deviation)	3.00 (± 1.767)	3.18 (± 2.183)	3.34 (± 2.512)	3.10 (± 3.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcomes : Quality of Life by Euro-QoL-5

End point title	Patient Reported Outcomes : Quality of Life by Euro-QoL-5

End point description:

Patient reported outcomes : Quality of Life by Euro-QoL-5 (day 28 and day 90).
Change 1 = Visual analog scale (VAS) at discharge - VAS at day 90.
Change 2 = VAS at day 28 - VAS at day 90

End point type	Secondary

End point timeframe:

day 28 and day 90

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72[20]	77[21]	152[22]	149[23]
Units: score on a scale				
arithmetic mean (standard deviation)				
Change 1	-13.4 (± 22.11)	-19.3 (± 22.76)	57.3 (± 22.09)	-16.5 (± 22.45)
Change 2	-11.8 (± 16.21)	-10.2 (± 19.40)	-5.9 (± 21.50)	-11.0 (± 17.83)

Notes:

[20] - Change 1, 27 subjects analysed
Change 2, 30 subjects analysed
[21] - Change 1, 30 subjects analysed
Change 2, 33 subjects analysed
[22] - Change 1, 71 subjects analysed
Change 2, 65 subjects analysed
[23] - Change 1, 57 subjects analysed
Change 2, 63 subjects analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs

End point title	Vital Signs

End point description:

Vital signs: heart rate (beat per minute), blood pressure - mean arterial pressure (MAP) mmHg Change from baseline to Day 7.

End point type	Secondary

End point timeframe:

7 days

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	39	46	80	85
Units: beats per minute / mmHg				
arithmetic mean (standard deviation)				
Heart rate change day 7 (maximum)	6.1 (± 33.52)	4.8 (± 21.11)	13.5 (± 28.25)	5.4 (± 27.34)
Heart rate change day 7 (minimum)	-26.8 (± 23.06)	-17.8 (± 19.90)	-18.1 (± 24.49)	-21.9 (± 21.75)
MAP change day 7 (maximum)	30.2 (± 22.06)	27.6 (± 16.31)	31.7 (± 21.09)	28.8 (± 19.09)
MAP change day 7 (minimum)	-9.3 (± 17.34)	-6.0 (± 10.86)	-8.7 (± 18.97)	-7.5 (± 14.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Penalized Sepsis Support Index (pSSI) at 28 Day Follow-up

End point title	Penalized Sepsis Support Index (pSSI) at 28 Day Follow-up

End point description:

Penalized Sepsis Support Index (pSSI) at 28 day follow-up, defined similar to the SSI with the exception that patients that die get penalized by assigning the maximum value, i.e. the pSSI is set to 14 or 28, respectively. Minimum value possible is 0, maximum value is 14. A higher score means a worse outcome.

End point type	Secondary

End point timeframe:

day 28

End point values	Treatment Arm A	Treatment Arm B	Control Group	Adrecizumab Overall
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	75	151	145
Units: score on a scale				
arithmetic mean (standard deviation)	13.8 (± 11.34)	14.8 (± 10.87)	13.2 (± 11.36)	14.3 (± 11.07)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: In Sub-study Key Pharmacokinetic Parameters Peak Plasma Concentrations (Cmax) Are to be Determined in 80 Patients

End point title	In Sub-study Key Pharmacokinetic Parameters Peak Plasma Concentrations (Cmax) Are to be Determined in 80 Patients[24]

End point description:

Peak plasma concentrations (Cmax). Samples taken prior IMP administration, at 30 min, 24 hrs, 48 hrs , 96 hrs, 144 hrs, 648 hrs after Infusion.

End point type	Other pre-specified

End point timeframe:

28 days

Notes:

[24] - 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: The pharmacokinetic parameter is measured in the treatment groups only

End point values	Treatment Arm A	Treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	29		
Units: µg/mL				
arithmetic mean (standard deviation)	38.193 (± 10.3942)	86.854 (± 22.2438)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: In Sub-study Key Pharmacokinetic Parameters Time to Cmax (Tmax) Are to be Determined in 80 Patients

End point title	In Sub-study Key Pharmacokinetic Parameters Time to Cmax (Tmax) Are to be Determined in 80 Patients[25]

End point description:

Time to Cmax (tmax) in hours (h)

End point type	Other pre-specified

End point timeframe:

28 days

Notes:

[25] - 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: The pharmacokinetic parameter is measured in the treatment groups only

End point values	Treatment Arm A	Treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: Percent of participants				
number (not applicable)				
0.25 h	0	1		
0.37 h	1	0		
0.42 h	2	1		
0.45 h	0	1		
0.47 h	0	2		
0.5 h	17	18		

0.57 h	1	0		
0.58 h	2	2		
0.67 h	1	2		
0.73 h	0	1		
2.5 h	0	1		
21.97 h	0	1		
24.75 h	1	0		
25.12 h	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: In Sub-study Key Pharmacokinetic Parameter AUC is to be Determined in 80 Patients

End point title	In Sub-study Key Pharmacokinetic Parameter AUC is to be Determined in 80 Patients[26]

End point description:

Systemic exposure : Area under the plasma concentration versus time curve (AUC). Samples taken prior IMP administration, at 30 min, 24 hrs, 48 hrs , 96 hrs, 144 hrs, 648 hrs after Infusion.

End point type	Other pre-specified

End point timeframe:

28 days

Notes:

[26] - 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: The pharmacokinetic parameter is measured in the treatment groups only

End point values	Treatment Arm A	Treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: h*µg/mL				
arithmetic mean (standard deviation)	4910.33 (± 1222.414)	11245.288 (± 3462.585)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: In Sub-study Key Pharmacokinetic Parameter Systemic Clearance is to be Determined in 80 Patients

End point title	In Sub-study Key Pharmacokinetic Parameter Systemic Clearance is to be Determined in 80 Patients[27]

End point description:

systemic clearance (CL)prior IMP administration, at 30 min, 24 hrs, 48 hrs , 96 hrs, 144 hrs, 648 hrs after Infusion.

End point type	Other pre-specified

End point timeframe:

28 days

Notes:

[27] - 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: The pharmacokinetic parameter is measured in the treatment groups only

End point values	Treatment Arm A	Treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: L/h				
arithmetic mean (standard deviation)	0.0286 (± 0.00790)	0.0280 (± 0.00826)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: In Sub-study Key Pharmacokinetic Parameter Elimination Half-life is to be Determined in 80 Patients

End point title	In Sub-study Key Pharmacokinetic Parameter Elimination Half-life is to be Determined in 80 Patients[28]

End point description:

Elimination half-life (t½) prior IMP administration, at 30 min, 24 hrs, 48 hrs , 96 hrs, 144 hrs, 648 hrs after Infusion.

End point type	Other pre-specified

End point timeframe:

28 days

Notes:

[28] - 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: The pharmacokinetic parameter is measured in the treatment groups only

End point values	Treatment Arm A	Treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: hours				
arithmetic mean (standard deviation)	206.48 (± 43.809)	177.90 (± 44.250)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: In Sub-study Key Pharmacokinetic Parameter Volume of Distribution is to be Determined in 80 Patients

End point title	In Sub-study Key Pharmacokinetic Parameter Volume of Distribution is to be Determined in 80 Patients[29]

End point description:

Volume of distribution (V) prior IMP administration, at 30 min, 24 hrs, 48 hrs , 96 hrs, 144 hrs, 648 hrs after Infusion.

End point type	Other pre-specified

End point timeframe:

28 days

Notes:

[29] - 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: The pharmacokinetic parameter is measured in the treatment groups only

End point values	Treatment Arm A	Treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	29		
Units: Liter				
arithmetic mean (standard deviation)	4.277 (± 1.9220)	3.737 (± 0.9427)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events whether serious or non-serious and judged related or unrelated to the study drug occurring during the study period (Day 1 (inclusion) until 90 days after study drug administration) were collected. The study period was 2 years.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Treatment Arm A

Reporting group description:

Intravenous infusion over approximately 1 hour of single i.v. dose of 2 mg/kg Adrecizumab
Adrecizumab: Single i.v. dose of 2 mg/kg

Reporting group title	Treatment Arm B

Reporting group description:

Intravenous infusion over approximately 1 hour of single i.v. dose of 4 mg/kg Adrecizumab
Adrecizumab: Single i.v. dose of 4 mg/kg

Reporting group title	Control Group

Reporting group description:

Intravenous infusion over approximately 1 hour of single i.v. dose of Placebo of Adrecizumab
Placebo: Single i.v. dose of placebo

Serious adverse events	Treatment Arm A	Treatment Arm B	Control Group
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 72 (63.89%)	42 / 77 (54.55%)	96 / 152 (63.16%)
number of deaths (all causes)	26	24	54
number of deaths resulting from adverse events	26	24	54
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Neoplasm progression			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Arteriovenous fistula			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Circulatory collapse			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Hypotension			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			

subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Shock haemorrhagic			
subjects affected / exposed	4 / 72 (5.56%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Withdrawal of life support			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Critical illness			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Death			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

General physical health deterioration			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	3 / 152 (1.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Impaired healing			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multimorbidity			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 72 (5.56%)	7 / 77 (9.09%)	11 / 152 (7.24%)
occurrences causally related to treatment / all	0 / 4	1 / 7	0 / 11
deaths causally related to treatment / all	0 / 4	0 / 5	0 / 11
Pyrexia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 72 (2.78%)	2 / 77 (2.60%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aspiration			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Bronchospasm			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal haemorrhage			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	1 / 72 (1.39%)	2 / 77 (2.60%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Pulmonary oedema			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			

subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 72 (1.39%)	5 / 77 (6.49%)	7 / 152 (4.61%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Respiratory fatigue			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Embedded device			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 72 (0.00%)	2 / 77 (2.60%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endotracheal intubation complication			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eschar			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal anastomosis complication			
subjects affected / exposed	0 / 72 (0.00%)	2 / 77 (2.60%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weaning failure			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 72 (1.39%)	3 / 77 (3.90%)	3 / 152 (1.97%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 72 (0.00%)	2 / 77 (2.60%)	4 / 152 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 72 (1.39%)	2 / 77 (2.60%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Conduction disorder			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve incompetence			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular hypokinesia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 72 (2.78%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Depressed level of consciousness			

subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osmotic demyelination syndrome			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Seizure			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Status epilepticus			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic necrosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 72 (1.39%)	4 / 77 (5.19%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Fistula of small intestine			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Gastric ulcer			

subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal perforation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ileus paralytic			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 77 (2.60%)	4 / 152 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Hepatic failure			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic necrosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema blister			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin necrosis			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 72 (2.78%)	2 / 77 (2.60%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal haematoma			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Primary adrenal insufficiency			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acinetobacter bacteraemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Clostridium colitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enterococcal sepsis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia peritonitis			

subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Gangrene			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Herpes sepsis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			

subjects affected / exposed	1 / 72 (1.39%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocarditis septic			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Necrotising fasciitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Peritonitis			
subjects affected / exposed	1 / 72 (1.39%)	2 / 77 (2.60%)	3 / 152 (1.97%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pneumonia			
subjects affected / exposed	4 / 72 (5.56%)	1 / 77 (1.30%)	3 / 152 (1.97%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Septic shock			
subjects affected / exposed	9 / 72 (12.50%)	15 / 77 (19.48%)	26 / 152 (17.11%)
occurrences causally related to treatment / all	0 / 10	0 / 16	1 / 26
deaths causally related to treatment / all	0 / 4	0 / 9	0 / 17
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Urosepsis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound abscess			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 77 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlactacidaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 77 (0.00%)	0 / 152 (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
Hypoglycaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 77 (1.30%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	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	Treatment Arm A	Treatment Arm B	Control Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 72 (94.44%)	77 / 77 (100.00%)	143 / 152 (94.08%)
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	44 / 72 (61.11%)	68 / 77 (88.31%)	84 / 152 (55.26%)
occurrences (all)	47	69	86
Diarrhoea			
subjects affected / exposed	6 / 72 (8.33%)	6 / 77 (7.79%)	8 / 152 (5.26%)
occurrences (all)	6	6	9
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	5 / 72 (6.94%)	8 / 77 (10.39%)	3 / 152 (1.97%)
occurrences (all)	5	8	3
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	11 / 72 (15.28%)	14 / 77 (18.18%)	12 / 152 (7.89%)
occurrences (all)	12	14	12
Hypernatraemia			
subjects affected / exposed	5 / 72 (6.94%)	12 / 77 (15.58%)	13 / 152 (8.55%)
occurrences (all)	5	12	13
Hypokalaemia			
subjects affected / exposed	11 / 72 (15.28%)	10 / 77 (12.99%)	24 / 152 (15.79%)
occurrences (all)	13	10	24
Hypophosphataemia			
subjects affected / exposed	6 / 72 (8.33%)	6 / 77 (7.79%)	17 / 152 (11.18%)
occurrences (all)	6	7	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2017	Changes in conduct or managment of the trial: • Extension of enrolment period due to slow recruitment from 18 months to 24 months • Revised Exclusion Criteria as days until death are difficult to assess; moribund is sufficient • Revised Exclusion Criteria: Typical sepsis patients may be also immunosuppressed • Deleted Exclusion Criteria: Typical sepsis patients may be also immunosuppressed /treated with immunosuppressants • Trial design updated to reflect the revised schedule of blood sampling • Clarification of evaluation of SOFA score • Clarification of timepoint for primary efficacy endpoint. • Revision of placebo ingredients • Clarification of safety endpoints • Clarification of endpoint regarding mechanical ventilation • Study endpoint APACHE II score removed as APACHE II score is only assessed at baseline • Study flow chart updated based on PAMv4.1 • Clarification of biomarker sampling • Revised schedule for determination of PaO2/FiO2 according to clinical routine. • Inclusion criteria updated to include the following o 6. Women of childbearing potential must have a negative serum or urine pregnancy test before randomization. o 7.Highly effective method of contraception must be maintained for 6 months after study start by women of childbearing potential and sexually active men. o 8. No care limitation • New section added to follow up screen failure patients • Added option for consent process of unconscious patients • Telephone Euro-QoL-5 Quality of Life Short Form added to the Section Discontinuation of Individual Patients • Clarified treatment of ongoing AEs and SAEs • New section added regarding retrospective ICF • Clarified the use of the Glasgow Coma Score • Clarification regarding timepoints for blood sampling for PK • Revised statistical plans outlined in the protocol • Further clarifications regarding role and responsibilities of DSMB and DSMB proce

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported