



Clinical trial results:

Phase IV, multicenter, prospective, randomized, open-label, controlled study on Landiolol in patients with septic shock resident in an Intensive Care Unit (LANDI-SEP)

Summary

EudraCT number	2017-002138-22
Trial protocol	AT DE CZ SI HU LT PL EE IT
Global end of trial date	16 February 2022

Results information

Result version number	v1 (current)
This version publication date	24 May 2023
First version publication date	24 May 2023

Trial information

Trial identification

Sponsor protocol code	LDLL300.401
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals GmbH
Sponsor organisation address	Leopold-Ungar-Platz 2, Wien, Austria, A-1190
Public contact	Clinical Operations, AOP Orphan Pharmaceuticals GmbH, 0043 6649639345, landi-sep@aoporphan.com
Scientific contact	Clinical Operations, AOP Orphan Pharmaceuticals GmbH, 0043 6649639345, landi-sep@aoporphan.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 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2022
Global end of trial reached?	Yes
Global end of trial date	16 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the rate of patients with heart rate response (i.e. HR = 80-94 bpm) and maintenance thereof without increase in vasopressor requirements in the first 24 hours after treatment start in a septic shock population with persistent tachycardia (≥ 95 bpm) randomized to either Group L or Group C.

Group L: will receive standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor treatment

And

Group C: will receive standard treatment according to SSCG 2016 which is not specifically targeted to the HR control

Protection of trial subjects:

The Investigator obtained a freely given signed ICF, with name and date noted by the patient/patient legal representative before the patient was exposed to any study-related procedure (or other country-specific documentation, as required). The study was carried out in compliance with the principles of Good Clinical Practice (GCP), data protection and confidentiality were handled in compliance with local laws.

Background therapy:

All patients received standard treatment according to SSCG 2016 which is not specifically targeted to the HR control. After study discontinuation patients received standard treatment according to their medical need and institutional policy.

Evidence for comparator: -

Actual start date of recruitment	27 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Czechia: 106
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Slovenia: 1
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	83
From 65 to 84 years	106
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

The study population comprised adult patients in the ICU with septic shock, who remained tachycardic and required vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg after a haemodynamic optimization period. Patients who fulfilled all the inclusion criteria and none of the exclusion criteria were eligible to participate.

Pre-assignment

Screening details:

Of 200 enrolled patients, 4 were not treated, one patient in Group L due to screening failure, while 2 patients in Group C were withdrawn due to the use of beta-blockers and one patient in Group C withdrew consent.

Period 1

Period 1 title	Overall treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group L

Arm description:

Patients in Group L received standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor treatment.

Arm type	Experimental
Investigational medicinal product name	LDLL300
Investigational medicinal product code	LDLL300
Other name	Landiolol hydrochloride
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Titration Phase (first 24 hours after treatment start):

- Starting dose 1 $\mu\text{g/kg/min}$
- Dose progressively increased at increments of 1 $\mu\text{g/kg/min}$ to a maximum of 40 $\mu\text{g/kg/min}$ with a minimum dose interval of 20 minutes in order to obtain a target HR of 80-94 bpm. LDLL300 must then be infused at any dose (1 $\mu\text{g/kg/min}$ to 40 $\mu\text{g/kg/min}$) to maintain target heart rate (HR).

Maintenance Phase I, II:

- LDLL300 had to be infused continuously to maintain a HR of 80–94 bpm for the duration of vasopressor infusion.

Arm title	Group C
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Arm description:

Patients in Group C received standard treatment according to SSCG 2016, which was not specifically targeted to the HR control.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Group L	Group C
Started	99	101
Treated (Safety set)	98	98
Full analysis set (FAS)	98	98
Per-protocol set (PPS)	87	89
Completed	54	49
Not completed	45	52
Adverse event, serious fatal	43	32
Consent withdrawn by subject	-	2
Discharge from site	-	1
Screening Failure	1	-
Administration of beta-blockers	-	17
Administration of beta-blocker	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group L
Reporting group description: Patients in Group L received standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor treatment.	
Reporting group title	Group C
Reporting group description: Patients in Group C received standard treatment according to SSCG 2016, which was not specifically targeted to the HR control.	

Reporting group values	Group L	Group C	Total
Number of subjects	99	101	200
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)	46	37	83
From 65-84 years	50	56	106
85 years and over	3	8	11
Age continuous			
Units: years			
median	66	68	
inter-quartile range (Q1-Q3)	57 to 74	56 to 76	-
Gender categorical			
Units: Subjects			
Female	36	45	81
Male	63	56	119
Heart rate			
Units: beats per minute			
arithmetic mean	116.0	114.7	
standard deviation	± 14.79	± 14.34	-

Subject analysis sets

Subject analysis set title	Group L FAS
Subject analysis set type	Full analysis
Subject analysis set description: All LDLL300 patients who entered the Treatment Phase	
Subject analysis set title	Group C FAS
Subject analysis set type	Full analysis
Subject analysis set description: All control group patients who entered the Treatment Phase	

Subject analysis set title	Group L PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients from the Group L FAS set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits.	
Subject analysis set title	Group C PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients from the Group C FAS set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits.	
Subject analysis set title	PK sub-study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PK sub-study included all patients enrolled in the sub-study, irrespective of any protocol violations, subsequent therapies, etc.	

Reporting group values	Group L FAS	Group C FAS	Group L PPS
Number of subjects	98	98	87
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)	46	36	39
From 65-84 years	49	54	45
85 years and over	3	8	3
Age continuous			
Units: years			
median	66	68	66
inter-quartile range (Q1-Q3)	57 to 74	56 to 76	57 to 75
Gender categorical			
Units: Subjects			
Female	35	43	33
Male	63	55	54
Heart rate			
Units: beats per minute			
arithmetic mean	116.0	114.2	116.0
standard deviation	± 14.86	± 13.5	± 14.4

Reporting group values	Group C PPS	PK sub-study	
Number of subjects	89	7	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	34	3	
From 65-84 years	47	4	
85 years and over	8	0	
Age continuous			
Units: years			
median	67	66	
inter-quartile range (Q1-Q3)	54 to 75	56 to 77	
Gender categorical			
Units: Subjects			
Female	38	3	
Male	51	4	
Heart rate			
Units: beats per minute			
arithmetic mean	114.6	109.3	
standard deviation	± 13.81	± 6.18	

End points

End points reporting groups

Reporting group title	Group L
Reporting group description: Patients in Group L received standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor treatment.	
Reporting group title	Group C
Reporting group description: Patients in Group C received standard treatment according to SSCG 2016, which was not specifically targeted to the HR control.	
Subject analysis set title	Group L FAS
Subject analysis set type	Full analysis
Subject analysis set description: All LDLL300 patients who entered the Treatment Phase	
Subject analysis set title	Group C FAS
Subject analysis set type	Full analysis
Subject analysis set description: All control group patients who entered the Treatment Phase	
Subject analysis set title	Group L PPS
Subject analysis set type	Per protocol
Subject analysis set description: Patients from the Group L FAS set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits.	
Subject analysis set title	Group C PPS
Subject analysis set type	Per protocol
Subject analysis set description: Patients from the Group C FAS set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits.	
Subject analysis set title	PK sub-study
Subject analysis set type	Sub-group analysis
Subject analysis set description: PK sub-study included all patients enrolled in the sub-study, irrespective of any protocol violations, subsequent therapies, etc.	

Primary: Heart rate response

End point title	Heart rate response
End point description: Heart rate response (i.e. HR = 80-94 bpm) and maintenance thereof and no increase in vasopressor requirements during the first 24 hours after treatment start.	
End point type	Primary
End point timeframe: First 24 hours after treatment start.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: count and percentage of patients				
responder	39	23	32	20
non-responder	59	75	55	69

Statistical analyses

Statistical analysis title	Primary response (FAS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group C FAS v Group L FAS
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0133 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	28.8

Notes:

[1] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[2] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Statistical analysis title	Primary response (PPS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0375 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	14.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	27.2

Notes:

[3] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[4] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Primary: Target heart rate reached

End point title	Target heart rate reached
End point description:	
Target heart rate reached (not necessarily maintained)	
End point type	Primary
End point timeframe:	
First 24 hours after treatment start.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: count and percentage of patients				
responder	74	42	65	38
non-responder	24	56	22	51

Statistical analyses

Statistical analysis title	Target heart rate reached (FAS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L FAS v Group C FAS
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	33
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.4
upper limit	44.9

Notes:

[5] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[6] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Statistical analysis title	Target heart rate reached (PPS)
Statistical analysis description: The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.0001 ^[8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	32.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.7
upper limit	44.7

Notes:

[7] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[8] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Primary: Target heart rate reached and maintained

End point title	Target heart rate reached and maintained
End point description:	
End point type	Primary
End point timeframe:	
First 24 hours after treatment start.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: Counts and percentages of patients				
responder	57	29	48	26
non-responder	41	69	39	63

Statistical analyses

Statistical analysis title	Target heart rate reached and maintained (FAS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L FAS v Group C FAS
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	< 0.0001 ^[10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	29
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.1
upper limit	41.3

Notes:

[9] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[10] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Statistical analysis title	Target heart rate reached and maintained (PPS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.0004 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	26.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.5
upper limit	39.2

Notes:

[11] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[12] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Primary: Vasopressors response

End point title	Vasopressors response
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End point description:

End point type	Primary
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End point timeframe:

First 24 hours after treatment start.

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: count and percentage of patients				
responder	56	65	48	60
non-responder	42	33	39	29

Statistical analyses

Statistical analysis title	Vasopressors response (FAS)
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Statistical analysis description:

The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.

Comparison groups	Group C FAS v Group L FAS
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Number of subjects included in analysis	196
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Analysis specification	Pre-specified
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Analysis type	superiority ^[13]
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P-value	= 0.1877 ^[14]
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Method	Cochran-Mantel-Haenszel
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Parameter estimate	Difference between the response rate
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Point estimate	-9.2
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-22
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upper limit	4.4
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Notes:

[13] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[14] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Statistical analysis title	Vasopressors response (PPS)
Statistical analysis description: The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.0971 ^[16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	2.1

Notes:

[15] - Hypothesis that Group L is superior to Group C in proportion of patients who reached the primary endpoint should have been demonstrated. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and supported by analysis using the PPS.

[16] - P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals.

Secondary: 28-day mortality

End point title	28-day mortality
End point description:	
End point type	Secondary
End point timeframe:	
Followed for 28 days.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	97	87	88
Units: count and percentage of patients				
alive	55	58	49	54
dead	43	39	38	34

Statistical analyses

Statistical analysis title	28-day mortality (FAS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L FAS v Group C FAS
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5954
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	17.3

Statistical analysis title	28-day mortality (PPS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4963
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.4
upper limit	19.2

Secondary: ICU mortality

End point title	ICU mortality
End point description:	
End point type	Secondary
End point timeframe:	
Observed during ICU stay, maximally 28 days.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	97	87	88
Units: count and percentage of patients				
did not die in ICU	55	64	49	60
died in ICU	43	33	38	28

Statistical analyses

Statistical analysis title	ICU mortality (FAS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L FAS v Group C FAS
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1592
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	23

Statistical analysis title	ICU mortality (PPS)
Statistical analysis description:	
The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel framework with stratification factor: the presence of atrial fibrillation.	
Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1066
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference between the response rate
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	25.6

Secondary: Duration of ICU stay

End point title	Duration of ICU stay
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End point description:

End point type	Secondary
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End point timeframe:

Observed during ICU stay, maximally 28 days.

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	58	49	54
Units: Number of patients				
Patients with risk events	41	36	37	33
Patients censored	14	22	12	21

Statistical analyses

Statistical analysis title	Duration of ICU stay (FAS)
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Statistical analysis description:

The duration of ICU stay for patients alive on Day 28 (FAS) was analyzed by KM analyses

Comparison groups	Group L FAS v Group C FAS
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Number of subjects included in analysis	113
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Analysis specification	Pre-specified
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Analysis type	other ^[17]
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P-value	= 0.4501
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Method	Logrank
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Parameter estimate	Hazard ratio (HR)
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Point estimate	1.17
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.7
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upper limit	1.94
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Notes:

[17] - The treatment groups were compared by log-rank test and by Cox proportional hazards model adjusted for strata and country.

Statistical analysis title	Duration of ICU stay (PPS)
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Statistical analysis description:

The duration of ICU stay for patients alive on Day 28 (PPS) was analyzed by KM analyses

Comparison groups	Group L PPS v Group C PPS
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Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 0.2201
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.89

Notes:

[18] - The treatment groups were compared by log-rank test and by Cox proportional hazards model adjusted for strata and country.

Secondary: Duration of hospital stay

End point title	Duration of hospital stay
End point description:	
End point type	Secondary
End point timeframe:	
Observed during hospital stay, maximally 28 days.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	58	49	54
Units: Number of patients				
Patients with risk events	21	22	19	21
Patients censored	34	36	30	33

Statistical analyses

Statistical analysis title	Duration of hospital stay (FAS)
Statistical analysis description:	
The duration of hospital stay for patients alive on Day 28 (FAS) was analyzed by KM.	
Comparison groups	Group L FAS v Group C FAS
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other ^[19]
P-value	= 0.541
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.54

Notes:

[19] - The treatment groups were compared by log-rank test and by Cox proportional hazards model adjusted for strata and site.

Statistical analysis title	Duration of hospital stay (PPS)
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Statistical analysis description:

The duration of ICU stay for patients alive on Day 28 (PPS) was analyzed by KM analyses.

Comparison groups	Group L PPS v Group C PPS
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other ^[20]
P-value	= 0.6128
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.58

Notes:

[20] - The treatment groups were compared by log-rank test and by Cox proportional hazards model adjusted for strata and site.

Secondary: Duration of inotropic agents administration

End point title	Duration of inotropic agents administration
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End point description:

End point type	Secondary
End point timeframe:	
Collected for 28 days.	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	9	8	8
Units: days				
arithmetic mean (standard deviation)	3.95 (± 3.777)	1.32 (± 1.125)	4.32 (± 3.859)	1.44 (± 1.140)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of vasopressors administration

End point title	Duration of vasopressors administration
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End point description:

End point type	Secondary
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End point timeframe:

Collected during 28 days

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: days				
arithmetic mean (standard deviation)	5.64 (± 7.162)	5.08 (± 5.195)	5.61 (± 7.081)	5.1 (± 4.943)

Statistical analyses

No statistical analyses for this end point

Secondary: Norepinephrine equivalent score during the study

End point title	Norepinephrine equivalent score during the study
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End point description:

End point type	Secondary
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End point timeframe:

Collected over 28 days

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: VIS Goradia units				
arithmetic mean (standard error)				
0h	0.513946 (± 0.0510805)	0.518040 (± 0.0547365)	0.544443 (± 0.0561420)	0.553186 (± 0.0589340)
2h	0.573436 (± 0.0561367)	0.537376 (± 0.0577913)	0.601001 (± 0.0611337)	0.575618 (± 0.0621795)
6h	0.554409 (± 0.0560717)	0.524078 (± 0.0804836)	0.588178 (± 0.0612983)	0.562675 (± 0.0877773)
12h	0.557292 (± 0.0717239)	0.399428 (± 0.0494849)	0.595915 (± 0.0795850)	0.424476 (± 0.0534782)
18h	0.451069 (± 0.0625476)	0.336070 (± 0.0344439)	0.480277 (± 0.0698323)	0.354531 (± 0.0366686)
24h	0.419481 (± 0.0564124)	0.275125 (± 0.0290651)	0.443791 (± 0.0621965)	0.290147 (± 0.0310909)
Day 2	0.189134 (± 0.0335021)	0.141637 (± 0.0183737)	0.198689 (± 0.0371176)	0.145597 (± 0.0193707)

Day 3	0.151513 (± 0.0320536)	0.107320 (± 0.0198550)	0.160958 (± 0.0354671)	0.097535 (± 0.0168156)
Day 4	0.132283 (± 0.0322658)	0.089132 (± 0.0162132)	0.139398 (± 0.0358993)	0.082654 (± 0.0155257)
Day 5	0.131284 (± 0.0330258)	0.075184 (± 0.0152838)	0.138727 (± 0.0367046)	0.079108 (± 0.0160554)
Day 6	0.097706 (± 0.0276469)	0.061453 (± 0.0145188)	0.099180 (± 0.0304038)	0.063878 (± 0.0153022)
Day 7	0.068789 (± 0.0194333)	0.054779 (± 0.0130981)	0.070819 (± 0.0215148)	0.057068 (± 0.0138369)
Day 8	0.057049 (± 0.0174820)	0.034539 (± 0.0109972)	0.060678 (± 0.0194773)	0.034588 (± 0.0115504)
Day 9	0.045864 (± 0.0140325)	0.031250 (± 0.0105587)	0.048523 (± 0.0154475)	0.031135 (± 0.0110969)
Day 10	0.039175 (± 0.0135977)	0.023029 (± 0.0088760)	0.042568 (± 0.0150135)	0.023217 (± 0.0094064)
Day 11	0.039491 (± 0.0149481)	0.025248 (± 0.0097517)	0.043422 (± 0.0165612)	0.024864 (± 0.0102546)
Day 12	0.046722 (± 0.0204517)	0.023384 (± 0.0097122)	0.052011 (± 0.0226728)	0.022492 (± 0.0101579)
Day 13	0.051713 (± 0.0244862)	0.018421 (± 0.0092893)	0.056779 (± 0.0271860)	0.015578 (± 0.0091613)
Day 14	0.059231 (± 0.0304127)	0.015985 (± 0.0088816)	0.064678 (± 0.0337859)	0.013787 (± 0.0090097)
Day 15	0.020118 (± 0.0089256)	0.013258 (± 0.0081590)	0.021384 (± 0.0099027)	0.012800 (± 0.0086844)
Day 16	0.016653 (± 0.0090859)	0.016522 (± 0.0091899)	0.017695 (± 0.0101389)	0.014438 (± 0.0093958)
Day 17	0.012578 (± 0.0049916)	0.016793 (± 0.0094318)	0.012792 (± 0.0054670)	0.013622 (± 0.0092375)
Day 18	0.014673 (± 0.0058270)	0.010785 (± 0.0089038)	0.014384 (± 0.0062576)	0.009375 (± 0.0093753)
Day 19	0.013145 (± 0.0051523)	0.005685 (± 0.0050649)	0.012023 (± 0.0051902)	0.005430 (± 0.0054299)
Day 20	0.012498 (± 0.0048658)	0.003963 (± 0.0035688)	0.012712 (± 0.0053304)	0.003837 (± 0.0038372)
Day 21	0.012544 (± 0.0064057)	0.005881 (± 0.0052506)	0.013570 (± 0.0071688)	0.005639 (± 0.0056392)
Day 22	0.011009 (± 0.0056418)	0.004336 (± 0.0039999)	0.012254 (± 0.0063158)	0.004318 (± 0.0043176)
Day 23	0.010585 (± 0.0053607)	0.004054 (± 0.0037406)	0.011509 (± 0.0060131)	0.004038 (± 0.0040377)
Day 24	0.009508 (± 0.0041469)	0.006521 (± 0.0046498)	0.010416 (± 0.0046467)	0.004201 (± 0.0042014)
Day 25	0.007027 (± 0.0028274)	0.004909 (± 0.0049091)	0.007554 (± 0.0031596)	0.005216 (± 0.0052159)
Day 26	0.006836 (± 0.0029071)	0.007631 (± 0.0076306)	0.006985 (± 0.0032084)	0.008118 (± 0.0081176)
Day 27	0.005244 (± 0.0025158)	0.006885 (± 0.0068846)	0.005391 (± 0.0027936)	0.007334 (± 0.0073336)
Day 28	0.000188 (± 0.0001879)	0.000000 (± 0.0000000)	0.000211 (± 0.0002114)	0.000000 (± 0.0000000)

Statistical analyses

No statistical analyses for this end point

Secondary: The vasopressors used in the study

End point title	The vasopressors used in the study
End point description:	
Frequencies of the patients using vasopressors during the whole treatment period	
End point type	Secondary
End point timeframe:	
Collected for 28 days	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: Number of patients				
NOREPINEPHRINE	98	98	87	89
VASOPRESSIN	43	36	40	36
TERLIPRESSIN	6	4	5	3
DOPAMINE	4	4	3	3
EPINEPHRINE	3	4	3	3
ISOPRENALINE	0	1	0	1
PHENYLEPHRINE HYDROCHLORIDE	1	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: The inotropic agents used in the study

End point title	The inotropic agents used in the study
End point description:	
Frequencies of patients using inotropic agents during the whole treatment period	
End point type	Secondary
End point timeframe:	
Followed for 28 days	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: Number of patients				
DOBUTAMINE	4	6	4	6
LEVOSIMENDAN	4	1	3	0
MILRINONE	1	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Total dose of inotropic agents

End point title	Total dose of inotropic agents
End point description: Total dose of inotropic agents during the whole study	
End point type	Secondary
End point timeframe: whole study	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: mg				
arithmetic mean (standard deviation)				
DOBUTAMINE	1036.37 (± 1160.295)	215.41 (± 253.137)	1036.37 (± 1160.295)	215.41 (± 253.137)
LEVOSIMENDAN	18.04 (± 21.288)	0.98 (± 0.000)	21.90 (± 24.301)	0.00 (± 0.000)
MILRINONE	67.36 (± 0.000)	0.00 (± 0.000)	67.36 (± 0.000)	0.00 (± 0.000)

Statistical analyses

No statistical analyses for this end point

Secondary: Avarage dose of inotropic agents

End point title	Avarage dose of inotropic agents
End point description: Avarage dose of inotropic agents during the whole study	
End point type	Secondary
End point timeframe: the whole study	

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	98	98	87	89
Units: ug/kg/min				
arithmetic mean (standard deviation)				
DOBUTAMINE	3.612 (± 2.0953)	1.860 (± 1.9166)	3.612 (± 2.0953)	215.41 (± 253.137)
LEVOSIMENDAN	0.032 (± 0.0341)	0.026 (± 0)	0.025 (± 0.0381)	0 (± 0)
MILRINONE	0.137 (± 0)	0 (± 0)	0.137 (± 0)	0 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of treatment-emergent bradycardic episodes

End point title	Incidence rate of treatment-emergent bradycardic episodes
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End point description:

Incidence rate of treatment-emergent bradycardic episodes during the study

End point type	Secondary
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End point timeframe:

whole study period

End point values	Group L	Group C		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: bradycardic episodes	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: SOFA score by visit

End point title	SOFA score by visit
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End point description:

SOFA score by visit, collected over 28 days

End point type	Secondary
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End point timeframe:

Collected over 28 days

End point values	Group L FAS	Group C FAS	Group L PPS	Group C PPS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed				
Units: score item				
arithmetic mean (standard deviation)				
V0 - Baseline	12.6 (± 3.54)	12.1 (± 2.83)	12.6 (± 3.45)	12.3 (± 2.81)
V1 (0-24h) - Titration Phase	12.8 (± 3.98)	11.8 (± 3.42)	12.9 (± 3.76)	11.9 (± 3.47)

V2 (24-48h) - Maintenance Phase I	13 (\pm 3.82)	11.5 (\pm 3.38)	13.1 (\pm 3.72)	11.6 (\pm 3.48)
V3 (48-72h) - Maintenance Phase I	12.7 (\pm 4.16)	11.4 (\pm 3.3)	12.9 (\pm 4.12)	11.6 (\pm 3.27)
V4 (72-96h) - Maintenance Phase I	11.9 (\pm 4.95)	11.6 (\pm 3.23)	12 (\pm 4.99)	11.7 (\pm 3.07)
V7 (Day 7) - Maintenance Phase II	12.2 (\pm 4.31)	11 (\pm 2.96)	12.3 (\pm 4.06)	11 (\pm 3.01)
V10 (Day 10) - Maintenance Phase II	11.8 (\pm 4.37)	9.9 (\pm 3.39)	12.2 (\pm 4.14)	9.8 (\pm 3.49)
V13 (Day 13) - Maintenance Phase II	10.1 (\pm 4.44)	9.7 (\pm 3.3)	10.5 (\pm 4.44)	9.7 (\pm 3.5)
V16 (Day 16) - Maintenance Phase II	10.8 (\pm 4.12)	11.2 (\pm 6.46)	10.8 (\pm 4.4)	11 (\pm 7.44)
V19 (Day 19) - Maintenance Phase II	9.4 (\pm 3.96)	11.7 (\pm 4.04)	9.4 (\pm 4.28)	10.5 (\pm 4.95)
V22 (Day 22) - Maintenance Phase II	9.1 (\pm 3.44)	12.7 (\pm 7.37)	9.3 (\pm 3.68)	14 (\pm 9.9)
V25 (Day 25) - Maintenance Phase II	9.3 (\pm 4.23)	11.5 (\pm 6.36)	9.8 (\pm 4.36)	11.5 (\pm 6.36)
V28 (Day 28) - Maintenance Phase II	7.7 (\pm 4.23)	9.5 (\pm 3.54)	8 (\pm 4.56)	9.5 (\pm 3.54)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average dialytic clearance for Landiolol

End point title	Average dialytic clearance for Landiolol
End point description:	
End point type	Other pre-specified
End point timeframe:	
8 hours after sub-study start	

End point values	PK sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ml/min				
arithmetic mean (standard deviation)	47.57 (\pm 32.571)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average dialytic clearance for Landiolol M1

End point title	Average dialytic clearance for Landiolol M1
End point description:	
End point type	Other pre-specified
End point timeframe:	
8 hours after sub-study start	

End point values	PK sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ml/min				
arithmetic mean (standard deviation)	43.97 (± 11.440)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average dialytic clearance for Creatinine

End point title	Average dialytic clearance for Creatinine
End point description:	
End point type	Other pre-specified
End point timeframe:	
8 hours after sub-study start	

End point values	PK sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ml/min				
arithmetic mean (standard deviation)	44.03 (± 16.656)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average dialytic clearance for Urea

End point title	Average dialytic clearance for Urea
End point description:	
End point type	Other pre-specified
End point timeframe:	
8 hours after sub-study start	

End point values	PK sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ml/min				
arithmetic mean (standard deviation)	36.76 (\pm 14.936)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC for Landiolol 0-8h

End point title	AUC for Landiolol 0-8h
End point description:	
End point type	Other pre-specified
End point timeframe:	
8 hours after sub-study start	

End point values	PK sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ug.min/ml				
arithmetic mean (standard deviation)	285.92 (\pm 242.705)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC for Landiolol M1 0-8h

End point title	AUC for Landiolol M1 0-8h
End point description:	
End point type	Other pre-specified
End point timeframe:	
8 hours after sub-study start	

End point values	PK sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ug.min/ml				
arithmetic mean (standard deviation)	2368.74 (± 1765.649)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring over the course of the clinical trial from randomization until end of the study at Day 28 are collected, documented and reported. Follow-up of AEs is required after Day 28 Follow-up (V-FU) if the AE or its sequelae persist.

Adverse event reporting additional description:

Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator and the Sponsor's medical expert or his/her designated representative but only to a maximum of 30 days after Day 28 Follow-up (V-FU).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Group C
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Reporting group description:

Patients in Group C received standard treatment according to SSCG 2016, which was not specifically targeted to the HR control.

Reporting group title	Group L
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Reporting group description:

Patients in Group L received standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor treatment.

Serious adverse events	Group C	Group L	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 98 (53.06%)	54 / 98 (55.10%)	
number of deaths (all causes)	38	43	
number of deaths resulting from adverse events	38	43	
Vascular disorders			
Cerebral haemorrhage	Additional description: Cerebral haemorrhage		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Circulatory collapse	Additional description: Circulatory collapse		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dry gangrene	Additional description: Dry gangrene		

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis	Additional description: Extremity necrosis		
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability	Additional description: Haemodynamic instability		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia	Additional description: Peripheral ischaemia		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock	Additional description: Shock		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic	Additional description: Shock haemorrhagic		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Leg amputation	Additional description: Leg amputation		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Resuscitation	Additional description: Resuscitation		

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome	Additional description: Multiple organ dysfunction syndrome		
subjects affected / exposed	14 / 98 (14.29%)	19 / 98 (19.39%)	
occurrences causally related to treatment / all	0 / 14	0 / 19	
deaths causally related to treatment / all	0 / 14	0 / 19	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	Additional description: Acute respiratory distress syndrome		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial haemorrhage	Additional description: Bronchial haemorrhage		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder	Additional description: Respiratory disorder		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure	Additional description: Respiratory failure		
subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	

Psychiatric disorders			
Delirium	Additional description: Delirium		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak	Additional description: Anastomotic leak		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal procedural complication	Additional description: Gastrointestinal procedural complication		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic rupture	Additional description: Hepatic rupture		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication	Additional description: Post procedural complication		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoplegia syndrome	Additional description: Vasoplegia syndrome		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Weaning failure	Additional description: Weaning failure		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation	Additional description: Atrial fibrillation		

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter	Additional description: Atrial flutter		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Cardiac arrest		
subjects affected / exposed	4 / 98 (4.08%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder	Additional description: Cardiac disorder		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute	Additional description: Cardiac failure acute		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock	Additional description: Cardiogenic shock		
subjects affected / exposed	3 / 98 (3.06%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiopulmonary failure	Additional description: Cardiopulmonary failure		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Low cardiac output syndrome	Additional description: Low cardiac output syndrome		

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus node dysfunction	Additional description: Sinus node dysfunction		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia	Additional description: Tachyarrhythmia		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation	Additional description: Ventricular fibrillation		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury	Additional description: Brain injury		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Disturbance in attention	Additional description: Disturbance in attention		

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke	Additional description: Ischaemic stroke		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal necrosis	Additional description: Gastrointestinal necrosis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication	Additional description: Intestinal anastomosis complication		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula	Additional description: Intestinal fistula		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia	Additional description: Intestinal ischaemia		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Intra-abdominal haemorrhage	Additional description: Intra-abdominal haemorrhage		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage	Additional description: Oesophageal haemorrhage		

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma	Additional description: Pancreatic carcinoma		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure	Additional description: Acute hepatic failure		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gallbladder rupture	Additional description: Gallbladder rupture		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure	Additional description: Hepatic failure		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Perforation bile duct	Additional description: Perforation bile duct		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abdominal sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Abdominal sepsis		
	1 / 98 (1.02%)	0 / 98 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
COVID-19 pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: COVID-19 pneumonia		
	0 / 98 (0.00%)	1 / 98 (1.02%)	
	0 / 0	0 / 1	
	0 / 0	0 / 1	
Necrotising fasciitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Necrotising fasciitis		
	1 / 98 (1.02%)	0 / 98 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
Peritonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Peritonitis		
	1 / 98 (1.02%)	0 / 98 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pneumonia		
	3 / 98 (3.06%)	0 / 98 (0.00%)	
	0 / 3	0 / 0	
	0 / 3	0 / 0	
Septic shock subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Septic shock		
	9 / 98 (9.18%)	11 / 98 (11.22%)	
	0 / 9	0 / 11	
	0 / 7	0 / 9	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Hyperkalaemia		
	0 / 98 (0.00%)	1 / 98 (1.02%)	
	0 / 0	0 / 1	
	0 / 0	0 / 1	

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

Non-serious adverse events	Group C	Group L	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 98 (32.65%)	33 / 98 (33.67%)	
Vascular disorders			
Arterial occlusive disease	Additional description: Arterial occlusive disease		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Haemodynamic instability	Additional description: Haemodynamic instability		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hypoperfusion	Additional description: Hypoperfusion		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	3 / 98 (3.06%)	9 / 98 (9.18%)	
occurrences (all)	5	9	
Jugular vein thrombosis	Additional description: Jugular vein thrombosis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Poor peripheral circulation	Additional description: Poor peripheral circulation		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Peripheral ischaemia	Additional description: Peripheral ischaemia		
subjects affected / exposed	1 / 98 (1.02%)	4 / 98 (4.08%)	
occurrences (all)	2	4	
Venous thrombosis	Additional description: Venous thrombosis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Leg amputation	Additional description: Leg amputation		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Multiple organ dysfunction syndrome subjects affected / exposed occurrences (all)	Additional description: Multiple organ dysfunction syndrome		
	0 / 98 (0.00%)	2 / 98 (2.04%)	
	0	2	
Pyrexia subjects affected / exposed occurrences (all)	Additional description: Pyrexia		
	1 / 98 (1.02%)	1 / 98 (1.02%)	
	1	1	
Respiratory, thoracic and mediastinal disorders			
	Additional description: Acute respiratory distress syndrome		
	0 / 98 (0.00%)	2 / 98 (2.04%)	
	0	2	
	Additional description: Atelectasis		
	1 / 98 (1.02%)	0 / 98 (0.00%)	
	1	0	
	Additional description: Bronchial disorder		
	1 / 98 (1.02%)	0 / 98 (0.00%)	
	1	0	
	Additional description: Hydrothorax		
	2 / 98 (2.04%)	1 / 98 (1.02%)	
	2	1	
	Additional description: Epistaxis		
	1 / 98 (1.02%)	0 / 98 (0.00%)	
	1	0	
	Additional description: Pleural effusion		
	4 / 98 (4.08%)	1 / 98 (1.02%)	
	4	1	
	Additional description: Pneumothorax		
	0 / 98 (0.00%)	1 / 98 (1.02%)	
	0	1	
	Additional description: Pulmonary hypertension		
	0 / 98 (0.00%)	1 / 98 (1.02%)	
	0	1	
	Additional description: Pulmonary embolism		
	0 / 98 (0.00%)	1 / 98 (1.02%)	
	0	1	
	Additional description: Respiratory failure		

subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences (all)	5	2	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Delirium	Additional description: Delirium		
subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences (all)	4	1	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hallucination	Additional description: Hallucination		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Investigations			
Blood lactic acid increased	Additional description: Blood lactic acid increased		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Blood pressure decreased	Additional description: Blood pressure decreased		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Heart rate decreased	Additional description: Heart rate decreased		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Oxygen saturation decreased	Additional description: Oxygen saturation decreased		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased	Additional description: Hepatic enzyme increased		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Troponin increased	Additional description: Troponin increased		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pancreatic enzymes increased	Additional description: Pancreatic enzymes increased		

subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	0 / 98 (0.00%) 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence	Additional description: Abdominal wound dehiscence		
subjects affected / exposed occurrences (all)	2 / 98 (2.04%) 2	1 / 98 (1.02%) 1	
Intestinal anastomosis complication	Additional description: Intestinal anastomosis complication		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	0 / 98 (0.00%) 0	
Post procedural haemorrhage	Additional description: Post procedural haemorrhage		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Cardiac disorders			
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	0 / 98 (0.00%) 0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed occurrences (all)	7 / 98 (7.14%) 7	3 / 98 (3.06%) 3	
Atrial flutter	Additional description: Atrial flutter		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	1 / 98 (1.02%) 1	
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	4 / 98 (4.08%) 5	
Cardiac dysfunction	Additional description: Cardiac dysfunction		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Cardiovascular insufficiency	Additional description: Cardiovascular insufficiency		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 2	1 / 98 (1.02%) 1	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Mitral valve incompetence	Additional description: Mitral valve incompetence		

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Myopericarditis	Additional description: Myopericarditis		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	3 / 98 (3.06%)	1 / 98 (1.02%)	
occurrences (all)	3	1	
Ventricular fibrillation	Additional description: Ventricular fibrillation		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Ventricular tachycardia	Additional description: Ventricular tachycardia		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cerebral ischaemia	Additional description: Cerebral ischaemia		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Monoparesis	Additional description: Monoparesis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Intensive care unit acquired weakness	Additional description: Intensive care unit acquired weakness		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Seizure	Additional description: Seizure		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Transient ischaemic attack	Additional description: Transient ischaemic attack		

subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	2 / 98 (2.04%) 2	
Coagulopathy	Additional description: Coagulopathy		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	0 / 98 (0.00%) 0	
Disseminated intravascular coagulation	Additional description: Disseminated intravascular coagulation		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	3 / 98 (3.06%) 3	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	1 / 98 (1.02%) 1	
Gastrointestinal disorders			
Ascites	Additional description: Ascites		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Colitis	Additional description: Colitis		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	0 / 98 (0.00%) 0	
Gastrointestinal haemorrhage	Additional description: Gastrointestinal haemorrhage		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	1 / 98 (1.02%) 1	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0	2 / 98 (2.04%) 2	
Intra-abdominal haemorrhage	Additional description: Intra-abdominal haemorrhage		
subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1	0 / 98 (0.00%) 0	
Mouth haemorrhage	Additional description: Mouth haemorrhage		

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Pancreatitis	Additional description: Pancreatitis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Peptic ulcer	Additional description: Peptic ulcer		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Tooth disorder	Additional description: Tooth disorder		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic cirrhosis	Additional description: Hepatic cirrhosis		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hepatic failure	Additional description: Hepatic failure		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia	Additional description: Hyperbilirubinaemia		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Portal vein thrombosis	Additional description: Portal vein thrombosis		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash		
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Oliguria	Additional description: Oliguria		

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Haematuria	Additional description: Haematuria		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Polyuria	Additional description: Polyuria		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Bursitis	Additional description: Bursitis		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Aspergillus infection	Additional description: Aspergillus infection		
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Bacteraemia	Additional description: Bacteraemia		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Candida infection	Additional description: Candida infection		
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Clostridium difficile colitis	Additional description: Clostridium difficile colitis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Cytomegalovirus infection reactivation	Additional description: Cytomegalovirus infection reactivation		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Empyema	Additional description: Empyema		

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Disseminated tuberculosis	Additional description: Disseminated tuberculosis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Endocarditis	Additional description: Endocarditis		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Enterococcal infection	Additional description: Enterococcal infection		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis salmonella	Additional description: Gastroenteritis salmonella		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Herpes simplex pneumonia	Additional description: Herpes simplex pneumonia		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Infection	Additional description: Infection		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Intervertebral discitis	Additional description: Intervertebral discitis		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Muscle abscess	Additional description: Muscle abscess		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	3 / 98 (3.06%)	1 / 98 (1.02%)	
occurrences (all)	3	1	
Pneumonia staphylococcal	Additional description: Pneumonia staphylococcal		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection	Additional description: Postoperative wound infection		

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pseudomonas infection	Additional description: Pseudomonas infection		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Renal tuberculosis	Additional description: Renal tuberculosis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Septic shock	Additional description: Septic shock		
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	2	
Wound infection fungal	Additional description: Wound infection fungal		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Feeding intolerance	Additional description: Feeding intolerance		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Hypernatraemia	Additional description: Hypernatraemia		
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences (all)	2	1	
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2017	Protocol Amendment 1
03 January 2018	Protocol Amendment 2
28 May 2018	Protocol Amendment 3
10 October 2018	Protocol Amendment 4
03 April 2019	Protocol Amendment 5
19 August 2019	Protocol Amendment 6
11 January 2021	Protocol Amendment 7

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The definition of the primary endpoint was specified in more detail by sponsor compared to the initial definition in study protocol.

Notes: