# 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 |

### 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 (≥95bpm) 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 µg/kg/min
- Dose progressively increased at increments of 1 µg/kg/min to a maximum of 40 µg/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 µg/kg/min to 40 µg/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 |

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 Tratment 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<br>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<br>Units: years | | | |
| median | 66 | 68 | 66 |
| inter-quartile range (Q1-Q3) | 57 to 74 | 56 to 76 | 57 to 75 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 35 | 43 | 33 |
| Male | 63 | 55 | 54 |
| Heart rate<br>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<br>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 Tratment 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 |

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: count and percentage of patients | | | | |
| responder | 56 | 65 | 48 | 60 |
| non-responder | 42 | 33 | 39 | 29 |

## Statistical analyses

| Statistical analysis title | Vasopressors 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[13] |
| P-value | = 0.1877 [14] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference between the response rate |
| Point estimate | -9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22 |
| upper limit | 4.4 |

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, maximaly 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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Observed during ICU stay, maximaly 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) |
|---|---|

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 |
|---|---|
| Number of subjects included in analysis | 113 |
| Analysis specification | Pre-specified |
| Analysis type | other[17] |
| P-value | = 0.4501 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.94 |

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) |
|---|---|

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[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, maximaly 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) |
|---|---|

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 |

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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

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 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

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 |
|---|---|

End point description:

Incidence rate of treatment-emergent bradycardic episodes during the study

| End point type | Secondary |
|---|---|

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 |
|---|---|

End point description:

SOFA score by visit, collected over 28 days

| End point type | Secondary |
|---|---|

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

### Reporting groups

| | |
|---|---|
| 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 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.

| 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 | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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** | | | |

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

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 | | | |

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

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|---|---|---|---|
| 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 | | |

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

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|---|---|---|---|
| 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 | | |

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

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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: