



Clinical trial results:

STRONG-HF: Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP TestinG, of Heart Failure Therapies

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2018-000486-37 |
| Trial protocol | AT HR |
| Global end of trial date | 13 October 2022 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 29 December 2022 |
| First version publication date | 28 July 2022 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set This trial has been completed. Results need to be entered. |
| Summary attachment (see zip file) | Results unavailable (Unavailable results for Heart Initiative CHF201701 8Jul2022_signed.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CHF201701 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03412201 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Heart Initiative |
| Sponsor organisation address | 1426 NC Highway 54 Suite B, Durham, United States, 27713 |
| Public contact | Beth Davison, Heart Initiative, +1 919-699-0888, bdavisonheartinitiative@gmail.org |
| Scientific contact | Beth Davison, Heart Initiative, +1 919-699-0888, bdavisonheartinitiative@gmail.org |

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 | 13 October 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 October 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 October 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of optimization of medical therapy with beta-blocker; ACEi, ARB or ARNi; and MRAs on 180-day all-cause mortality or heart failure readmission in patients admitted with acute heart failure and clinical and biological signs of congestion.

Protection of trial subjects:

The study was in compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. Before enrolment, the study was approved by appropriate competent authorities and all sites obtained approval from the ethics committees. All patients provided written informed consent. A Data and Safety Monitoring Board assessed safety on an ongoing basis during the trial. All the local regulatory requirements pertinent to the safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 01 May 2018 |
| 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: 10 |
| Country: Number of subjects enrolled | Mozambique: 59 |
| Country: Number of subjects enrolled | Nigeria: 165 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Tunisia: 12 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Bulgaria: 43 |
| Country: Number of subjects enrolled | Slovakia: 33 |
| Country: Number of subjects enrolled | Serbia: 2 |
| Country: Number of subjects enrolled | Russian Federation: 703 |
| Country: Number of subjects enrolled | Argentina: 40 |
| Country: Number of subjects enrolled | Colombia: 1 |
| Worldwide total number of subjects | 1078 |
| EEA total number of subjects | 92 |

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) | 547 |
| From 65 to 84 years | 521 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between May 10, 2018 and Sept 23, 2022 from 87 hospitals in 14 countries.

Pre-assignment

Screening details:

A total of 1641 patients were screened, of whom 556 did not pass screening (533 did not meet eligibility criteria, 7 decided not to participate, and 16 did not provide a reason). 1085 patients were randomly assigned to treatment, 7 of whom were randomly assigned in error, such that 1078 patients were validly assigned to either high intensity care or

Period 1

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

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | High Intensity Care |

Arm description:

Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | beta-blocker, renin-angiotensin system blocker, mineralocorticoid receptor blocker |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.

| | |
|------------------|------------|
| Arm title | Usual Care |
|------------------|------------|

Arm description:

Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.

| | |
|--|---------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | heart failure medications |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.

| Number of subjects in period 1 | High Intensity Care | Usual Care |
|---------------------------------------|---------------------|------------|
| Started | 542 | 536 |
| Completed | 467 | 459 |
| Not completed | 75 | 77 |
| Adverse event, serious fatal | 40 | 48 |
| Study terminated | 25 | 23 |
| Other reason | 10 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | High Intensity Care |
|-----------------------|---------------------|

Reporting group description:

Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.

| | |
|-----------------------|------------|
| Reporting group title | Usual Care |
|-----------------------|------------|

Reporting group description:

Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.

| Reporting group values | High Intensity Care | Usual Care | Total |
|--|---------------------|------------|-------|
| Number of subjects | 542 | 536 | 1078 |
| 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) | 273 | 274 | 547 |
| From 65-84 years | 261 | 260 | 521 |
| 85 years and over | 8 | 2 | 10 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62.9 | 63.0 | |
| standard deviation | ± 13.5 | ± 13.7 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 216 | 200 | 416 |
| Male | 326 | 336 | 662 |
| Race | | | |
| Units: Subjects | | | |
| Black | 115 | 115 | 230 |
| White or Caucasian | 418 | 414 | 832 |
| Native American | 1 | 0 | 1 |
| Other | 7 | 5 | 12 |
| Pacific Islander | 1 | 0 | 1 |
| Missing | 0 | 2 | 2 |
| Left ventricular ejection fraction category | | | |
| Units: Subjects | | | |
| ≤40% | 365 | 366 | 731 |
| >40% | 177 | 170 | 347 |
| Region of Enrollment | | | |
| Units: Subjects | | | |

| | | | |
|---------------|-----|-----|-----|
| Africa | 122 | 118 | 240 |
| Europe | 47 | 47 | 94 |
| Russia | 351 | 352 | 703 |
| South America | 22 | 19 | 41 |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | High Intensity Care |
| Reporting group description: Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses. | |
| Reporting group title | Usual Care |
| Reporting group description: Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards. | |

Primary: 180-day All-cause Mortality or Heart Failure Readmission

| | |
|--|--|
| End point title | 180-day All-cause Mortality or Heart Failure Readmission |
| End point description: Cumulative risk of either readmission for heart failure or death at 180 days | |
| End point type | Primary |
| End point timeframe: 180 days | |

| End point values | High Intensity Care | Usual Care | | |
|--|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 506 ^[1] | 502 ^[2] | | |
| Units: Weighted Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 15.2 | 23.3 | | |

Notes:

[1] - All patients randomized at sites that followed patients to day 180.

[2] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Primary Outcome |
| Statistical analysis description: 180-day All-cause Mortality or Heart Failure Readmission | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1008 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.0021 ^[4] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 8.1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.9 |
| upper limit | 13.2 |

Notes:

[3] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF ($\leq 40\%$ vs $>40\%$) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early cohort proportional to half its sample size.

[4] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Secondary: Change in Quality of Life

| | |
|---|---------------------------|
| End point title | Change in Quality of Life |
| End point description: | |
| Change from baseline to 90 days in quality of life as measured using the EQ-5D visual analogue scale (VAS) which ranges from 0 to 100 with a higher score representing a better outcome. "EQ-5D" is the official name of a quality of life instrument developed by EuroQol. | |
| End point type | Secondary |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 461 ^[5] | 454 ^[6] | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | 10.72 (\pm 0.88) | 7.22 (\pm 0.90) | | |

Notes:

[5] - Randomized patients with available data excluding subjects from Mozambique.

[6] - Randomized patients with available data excluding subjects from Mozambique.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in Quality of Life |
| Statistical analysis description: | |
| Change from baseline to 90 days in quality of life as measured using the EQ-5D visual analogue scale (VAS) which ranges from 0 to 100 with a higher score representing a better outcome. "EQ-5D" is the official name of a quality of life instrument developed by EuroQol. Subjects from Mozambique are excluded due to the unavailability of a linguistically validated translation of the EQ-5D in that country. | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 915 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[7] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3.49 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.74 |
| upper limit | 5.24 |

Notes:

[7] - Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF ($\leq 40\%$ vs $> 40\%$), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups.

Secondary: 180-day All-cause Mortality

| | |
|--------------------------------------|-----------------------------|
| End point title | 180-day All-cause Mortality |
| End point description: | |
| Cumulative risk of death at 180 days | |
| End point type | Secondary |
| End point timeframe: | |
| 180 days | |

| End point values | High Intensity Care | Usual Care | | |
|--|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 506 ^[8] | 502 ^[9] | | |
| Units: Weighted Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 8.48 | 10.04 | | |

Notes:

[8] - All patients randomized at sites that followed patients to day 180.

[9] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | 180-day All-cause Mortality |
| Statistical analysis description: | |
| Cumulative risk of death at 180 days | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1008 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.42 ^[11] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 5.4 |

Notes:

[10] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF ($\leq 40\%$ vs $> 40\%$) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early

cohort proportional to half its sample size.

[11] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Secondary: 90-day All-cause Mortality or Heart Failure Readmission

| | |
|---|---|
| End point title | 90-day All-cause Mortality or Heart Failure Readmission |
| End point description: | |
| Cumulative risk of either readmission for heart failure or death at 90 days | |
| End point type | Secondary |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 542 ^[12] | 536 ^[13] | | |
| Units: Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 10.4 | 13.8 | | |

Notes:

[12] - All patients validly randomized.

[13] - All patients validly randomized.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | 90-day All-cause Mortality or HF Readmission |
| Statistical analysis description: | |
| Cumulative risk of either readmission for heart failure or death at 90 days | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1078 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.081 ^[15] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 3.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 7.3 |

Notes:

[14] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF $\leq 40 / > 40$ using Mantel-Haenszel weights.

[15] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Other pre-specified: 180-day Cardiovascular Death

| | |
|--|------------------------------|
| End point title | 180-day Cardiovascular Death |
| End point description: | |
| Cumulative risk of death due to cardiovascular cause at 180 days | |
| End point type | Other pre-specified |

End point timeframe:

180 days

| End point values | High Intensity Care | Usual Care | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 506 ^[16] | 502 ^[17] | | |
| Units: Weighted Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 6.9 | 9.3 | | |

Notes:

[16] - All patients randomized at sites that followed patients to day 180.

[17] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

| Statistical analysis title | 180-day Cardiovascular Death |
|--|----------------------------------|
| Statistical analysis description: | |
| Cumulative risk of death due to cardiovascular cause at 180 days | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1008 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[18] |
| P-value | = 0.19 ^[19] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 6.1 |

Notes:

[18] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF ($\leq 40\%$ vs $>40\%$) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early cohort proportional to half its sample size.

[19] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Other pre-specified: 90-day Cardiovascular Death

| | |
|---|-----------------------------|
| End point title | 90-day Cardiovascular Death |
| End point description: | |
| Cumulative risk of death due to cardiovascular cause at 90 days | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 542 ^[20] | 536 ^[21] | | |
| Units: Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 3.3 | 5.4 | | |

Notes:

[20] - All patients validly randomized.

[21] - All patients validly randomized.

Statistical analyses

| Statistical analysis title | 90-day Cardiovascular Death |
|---|----------------------------------|
| Statistical analysis description: | |
| Cumulative risk of death due to cardiovascular cause at 90 days | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1078 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[22] |
| P-value | = 0.086 ^[23] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 4.6 |

Notes:

[22] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF ≤40/>40 using Mantel-Haenszel weights.

[23] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Other pre-specified: 90-day All-cause Mortality

| End point title | 90-day All-cause Mortality |
|-------------------------------------|----------------------------|
| End point description: | |
| Cumulative risk of death at 90 days | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 542 ^[24] | 536 ^[25] | | |
| Units: Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 4.3 | 5.7 | | |

Notes:

[24] - All patients validly randomized.

[25] - All patients validly randomized.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | 90-day All-cause Mortality |
| Statistical analysis description: | |
| Cumulative risk of death at 90 days | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1078 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[26] |
| P-value | = 0.28 ^[27] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 4 |

Notes:

[26] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF ≤40/>40 using Mantel-Haenszel weights.

[27] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Other pre-specified: 180-day Heart Failure Readmission

| | |
|--|-----------------------------------|
| End point title | 180-day Heart Failure Readmission |
| End point description: | |
| Cumulative risk of readmission for heart failure at 180 days | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 180 days | |

| End point values | High Intensity Care | Usual Care | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 506 ^[28] | 502 ^[29] | | |
| Units: Weighted Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 9.5 | 17.1 | | |

Notes:

[28] - All patients randomized at sites that followed patients to day 180.

[29] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

| | |
|--|-----------------------------------|
| Statistical analysis title | 180-day Heart Failure Readmission |
| Statistical analysis description: | |
| Cumulative risk of readmission for heart failure at 180 days | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 1008 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[30] |
| P-value | = 0.0011 ^[31] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 7.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3 |
| upper limit | 12.1 |

Notes:

[30] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF ($\leq 40\%$ vs $>40\%$) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early cohort proportional to half its sample size.

[31] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Other pre-specified: 90-day Heart Failure Readmission

| | |
|---|----------------------------------|
| End point title | 90-day Heart Failure Readmission |
| End point description: | |
| Cumulative risk of readmission for heart failure at 90 days | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 542 ^[32] | 536 ^[33] | | |
| Units: Adjusted KM Event Rate (%) | | | | |
| number (not applicable) | 6.9 | 9.5 | | |

Notes:

[32] - All patients validly randomized.

[33] - All patients validly randomized.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | 90-day Heart Failure Readmission |
| Statistical analysis description: | |
| Cumulative risk of readmission for heart failure at 90 days | |
| Comparison groups | High Intensity Care v Usual Care |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 1078 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[34] |
| P-value | = 0.13 ^[35] |
| Method | Chi-squared |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 5.8 |

Notes:

[34] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF ≤40/>40 using Mantel-Haenszel weights.

[35] - A chi-square test statistic with 1df computed as D^2/V , where D is the difference in event rates with associated variance V.

Other pre-specified: Finkelstein-Schoenfeld Hierarchical Composite

| | |
|--|---|
| End point title | Finkelstein-Schoenfeld Hierarchical Composite |
| End point description: | |
| Hierarchical composite endpoint comprising death, heart failure readmissions, and EQ-VAS analyzed using Finkelstein-Schoenfeld methodology | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 542 ^[36] | 536 ^[37] | | |
| Units: percentage of favorable comparisons | | | | |
| number (not applicable) | 40.4 | 29.4 | | |

Notes:

[36] - All patients validly randomized.

[37] - All patients validly randomized.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Finkelstein-Schoenfeld Hierarchical Composite |
| Statistical analysis description: | |
| Hierarchical composite endpoint comprising death, heart failure readmissions, and EQ-VAS analyzed using Finkelstein-Schoenfeld methodology. | |
| Comparison groups | High Intensity Care v Usual Care |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 1078 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[38] |
| P-value | = 0.0002 ^[39] |
| Method | van Elteren's test |
| Parameter estimate | Mann-Whitney odds |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.13 |
| upper limit | 1.46 |

Notes:

[38] - Treatment effect is the Mann-Whitney odds adjusted for LVEF ($\leq 40\%$ vs $>40\%$) and geographical region, using Mantel-Haenzsel weights.

[39] - P-value calculated from van Elteren's test stratified by LVEF ($\leq 40\%$ vs $>40\%$) and geographical region, using modified ridit scores.

Other pre-specified: Change in NT-proBNP

| | |
|---|---------------------|
| End point title | Change in NT-proBNP |
| End point description: | |
| Change from baseline to 90 days in NT-proBNP on the log scale | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 476 ^[40] | 475 ^[41] | | |
| Units: ratio | | | | |
| least squares mean (standard error) | 0.436 (\pm 1.072) | 0.564 (\pm 1.074) | | |

Notes:

[40] - Randomized patients with available data.

[41] - Randomized patients with available data.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in NT-proBNP |
| Statistical analysis description: | |
| Change from baseline to 90 days in NT-proBNP on the log scale | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 951 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[42] |
| P-value | = 0.0003 ^[43] |
| Method | ANCOVA |
| Parameter estimate | Adjusted Geometric Mean Ratio |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 0.89 |

Notes:

[42] - Comparison of the ratio of post-baseline value over the baseline value adjusted for the specified covariates between the high-intensity care group and the usual care group.

[43] - Statistics are estimated based on an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, LVEF ≤ 40 / >40 , region, and baseline log-transformed NT-proBNP value.

Other pre-specified: Change in Weight

| | |
|---|---------------------|
| End point title | Change in Weight |
| End point description: | |
| Change from baseline to 90 days in weight in kg | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 489 ^[44] | 479 ^[45] | | |
| Units: kg | | | | |
| least squares mean (standard error) | -1.78 (\pm 0.282) | -0.42 (\pm 0.290) | | |

Notes:

[44] - Randomized patients with available data.

[45] - Randomized patients with available data.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Change in Weight |
| Statistical analysis description: | |
| Change from baseline to 90 days in weight in kg | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 968 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[46] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.91 |
| upper limit | -0.8 |

Notes:

[46] - Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups.

Other pre-specified: Changes in Signs and Symptoms of Congestion: NYHA Class

| | |
|-----------------|---|
| End point title | Changes in Signs and Symptoms of Congestion: NYHA Class |
|-----------------|---|

End point description:

Changes from baseline to 90 days in New York Heart Association (NYHA) class which ranges from I to IV with a higher class representing a worse outcome.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

90 days

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 ^[47] | 488 ^[48] | | |
| Units: participants | | | | |
| NYHA at baseline: I | 34 | 27 | | |
| NYHA at baseline: II | 288 | 306 | | |
| NYHA at baseline: III | 170 | 152 | | |
| NYHA at baseline: IV | 3 | 3 | | |
| NYHA at day 90: I | 116 | 76 | | |
| NYHA at day 90: II | 297 | 288 | | |
| NYHA at day 90: III | 77 | 107 | | |
| NYHA at day 90: IV | 5 | 17 | | |

Notes:

[47] - Randomized patients with available data.

[48] - Randomized patients with available data.

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Changes in Signs and Symptoms of Congestion: NYHA |
|----------------------------|---|

Statistical analysis description:

Changes from baseline to 90 days in New York Heart Association (NYHA) class which ranges from I to IV with a higher class representing a worse outcome.

| | |
|-------------------|----------------------------------|
| Comparison groups | High Intensity Care v Usual Care |
|-------------------|----------------------------------|

| | |
|---|-----|
| Number of subjects included in analysis | 983 |
|---|-----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-----------------------------|
| Analysis type | superiority ^[49] |
|---------------|-----------------------------|

| | |
|---------|--------------------------|
| P-value | < 0.0001 ^[50] |
|---------|--------------------------|

| | |
|--------|--------------------|
| Method | van Elteren's test |
|--------|--------------------|

| | |
|--------------------|-------------------|
| Parameter estimate | Mann-Whitney odds |
|--------------------|-------------------|

| | |
|----------------|------|
| Point estimate | 1.36 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | 1.22 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 1.53 |
|-------------|------|

Notes:

[49] - Treatment effect presented as Mann-Whitney odds stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

A Mann-Whitney odds value of >1.0 favours high-intensity care.

[50] - P value from van Elteren's test stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: Orthopnea

| | |
|--|--|
| End point title | Changes in Signs and Symptoms of Congestion: Orthopnea |
| End point description: Changes from baseline to 90 days in orthopnea rated on a scale from 0 to 3 with a higher score representing a worse outcome. | |
| End point type | Other pre-specified |
| End point timeframe: 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 493 ^[51] | 486 ^[52] | | |
| Units: participants | | | | |
| 0: None at baseline | 308 | 304 | | |
| 1: 1 pillow (10 cm) at baseline | 168 | 165 | | |
| 2: 2 pillows (20 cm) at baseline | 16 | 16 | | |
| 3: >30 degrees at baseline | 1 | 1 | | |
| 0: None at day 90 | 381 | 339 | | |
| 1: 1 pillow (10 cm) at day 90 | 99 | 124 | | |
| 2: 2 pillows (20 cm) at day 90 | 10 | 19 | | |
| 3: >30 degrees at day 90 | 3 | 4 | | |

Notes:

[51] - Randomized patients with available data.

[52] - Randomized patients with available data.

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Changes in Orthopnea |
| Statistical analysis description: Changes from baseline to 90 days in orthopnea rated on a scale from 0 to 3 with a higher score representing a worse outcome. | |
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 979 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[53] |
| P-value | = 0.0048 ^[54] |
| Method | van Elteren's test |
| Parameter estimate | Mann-Whitney odds |
| Point estimate | 1.17 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.07 |
| upper limit | 1.29 |

Notes:

[53] - Treatment effect presented as Mann-Whitney odds stratified by LVEF ($\leq 40\%$ vs $> 40\%$), geographical region, and baseline value.

A Mann-Whitney odds value of > 1.0 favours high-intensity care.

[54] - P value from van Elteren's test stratified by LVEF ($\leq 40\%$ vs $> 40\%$), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: Peripheral Edema

| | |
|-----------------|---|
| End point title | Changes in Signs and Symptoms of Congestion: Peripheral Edema |
|-----------------|---|

End point description:

Changes from baseline to 90 days in peripheral edema rated on a scale from 0 to 3 with a higher score representing a worse.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

90 days

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 491 ^[55] | 483 ^[56] | | |
| Units: participants | | | | |
| None at baseline | 286 | 278 | | |
| 1+ at baseline | 175 | 173 | | |
| 2+ at baseline | 29 | 27 | | |
| 3+ at baseline | 1 | 5 | | |
| None at day 90 | 384 | 315 | | |
| 1+ at day 90 | 91 | 130 | | |
| 2+ at day 90 | 15 | 33 | | |
| 3+ at day 90 | 1 | 5 | | |

Notes:

[55] - Randomized patients with available data.

[56] - Randomized patients with available data.

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | Changes in Peripheral Edema |
|----------------------------|-----------------------------|

Statistical analysis description:

Changes from baseline to 90 days in peripheral edema rated on a scale from 0 to 3 with a higher score representing a worse outcome.

| | |
|-------------------|----------------------------------|
| Comparison groups | High Intensity Care v Usual Care |
|-------------------|----------------------------------|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 974 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[57] |
| P-value | = 0.0002 ^[58] |
| Method | van Elteren's test |
| Parameter estimate | Mann-Whitney odds |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.17 |
| upper limit | 1.44 |

Notes:

[57] - Treatment effect presented as Mann-Whitney odds stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

A Mann-Whitney odds value of >1.0 favours high-intensity care.

[58] - P value from van Elteren's test stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: Rales

| | |
|--|--|
| End point title | Changes in Signs and Symptoms of Congestion: Rales |
| End point description: | |
| Changes from baseline to 90 days in rales rated on a scale from 0 to 3 with a higher score representing a worse outcome. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 90 days | |

| End point values | High Intensity Care | Usual Care | | |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 490 ^[59] | 479 ^[60] | | |
| Units: participants | | | | |
| 0: None at baseline | 417 | 411 | | |
| 1: $<1/3$ at baseline | 63 | 63 | | |
| 2: $1/3$ to $2/3$ at baseline | 10 | 5 | | |
| 3: $>2/3$ at baseline | 0 | 0 | | |
| 0: None at day 90 | 454 | 421 | | |
| 1: $<1/3$ at day 90 | 33 | 57 | | |
| 2: $1/3$ to $2/3$ at day 90 | 3 | 1 | | |
| 3: $>2/3$ at day 90 | 0 | 0 | | |

Notes:

[59] - Randomized patients with available data.

[60] - Randomized patients with available data.

Statistical analyses

| | |
|--|------------------|
| Statistical analysis title | Changes in Rales |
| Statistical analysis description: | |
| Changes from baseline to 90 days in rales rated on a scale from 0 to 3 with a higher score representing a worse outcome. | |

| | |
|---|----------------------------------|
| Comparison groups | High Intensity Care v Usual Care |
| Number of subjects included in analysis | 969 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[61] |
| P-value | = 0.073 ^[62] |
| Method | van Elteren's test |
| Parameter estimate | Mann-Whitney odds |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 1.15 |

Notes:

[61] - Treatment effect presented as Mann-Whitney odds stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

A Mann-Whitney odds value of >1.0 favours high-intensity care.

[62] - P value from van Elteren's test stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: JVP

| | |
|------------------------|---|
| End point title | Changes in Signs and Symptoms of Congestion: JVP |
| End point description: | Changes from baseline to 90 days in jugular venous pulse (JVP) rated on a scale from 1 to 3 with a higher score representing a worse outcome. |
| End point type | Other pre-specified |
| End point timeframe: | 90 days |

| End point values | High Intensity Care | Usual Care | | |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 450 ^[63] | 428 ^[64] | | |
| Units: participants | | | | |
| 1: <6 cm at baseline | 383 | 359 | | |
| 2: 6–10 cm at baseline | 64 | 66 | | |
| 3: >10 cm at baseline | 3 | 3 | | |
| 1: <6 cm at day 90 | 418 | 377 | | |
| 2: 6–10 cm at day 90 | 30 | 40 | | |
| 3: >10 cm at day 90 | 2 | 11 | | |

Notes:

[63] - Randomized patients with available data.

[64] - Randomized patients with available data.

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Changes in JVP |
| Statistical analysis description: | Changes from baseline to 90 days in jugular venous pulse (JVP) rated on a scale from 1 to 3 with a higher score representing a worse outcome. |
| Comparison groups | High Intensity Care v Usual Care |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 878 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[65] |
| P-value | = 0.015 ^[66] |
| Method | van Elteren's test |
| Parameter estimate | Mann-Whitney odds |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.05 |
| upper limit | 1.21 |

Notes:

[65] - Treatment effect presented as Mann-Whitney odds stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

A Mann-Whitney odds value of >1.0 favours high-intensity care.

[66] - P value from van Elteren's test stratified by LVEF ($\leq 40\%$ vs $>40\%$), geographical region, and baseline value.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 90

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | High Intensity Care |
|-----------------------|---------------------|

Reporting group description:

Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.

| | |
|-----------------------|------------|
| Reporting group title | Usual Care |
|-----------------------|------------|

Reporting group description:

Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.

| Serious adverse events | High Intensity Care | Usual Care | |
|---|---------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 88 / 542 (16.24%) | 92 / 536 (17.16%) | |
| number of deaths (all causes) | 23 | 30 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Surgical and medical procedures | | | |

| | | | |
|--|-----------------|------------------|--|
| Chemotherapy | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| High frequency ablation | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sudden death | | | |
| subjects affected / exposed | 5 / 542 (0.92%) | 10 / 536 (1.87%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 10 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 542 (0.18%) | 3 / 536 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (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 | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 2 / 536 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 38 / 542 (7.01%) | 47 / 536 (8.77%) | |
| occurrences causally related to treatment / all | 0 / 42 | 0 / 52 | |
| deaths causally related to treatment / all | 0 / 7 | 0 / 10 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 2 / 536 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 6 / 536 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 2 / 536 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 4 / 542 (0.74%) | 2 / 536 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Hemianopia homonymous | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 2 / 536 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia strangulated | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis infective | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Corona virus infection | | | |
| subjects affected / exposed | 10 / 542 (1.85%) | 6 / 536 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 542 (0.74%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 7 / 542 (1.29%) | 3 / 536 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | High Intensity Care | Usual Care | |
|---|---------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 157 / 542 (28.97%) | 77 / 536 (14.37%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign gastric neoplasm | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 2 / 536 (0.37%) | |
| occurrences (all) | 3 | 2 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 4 / 542 (0.74%) | 2 / 536 (0.37%) | |
| occurrences (all) | 4 | 2 | |
| Hypotension | | | |
| subjects affected / exposed | 26 / 542 (4.80%) | 2 / 536 (0.37%) | |
| occurrences (all) | 33 | 2 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 0 / 536 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Surgical and medical procedures | | | |
| Chemotherapy | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 1 / 536 (0.19%) | |
| occurrences (all) | 2 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 2 / 536 (0.37%) 2 | |
| Pain subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Swelling subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Immune system disorders Amyloidosis subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Reproductive system and breast disorders Gynaecomastia subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Metrorrhagia subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 1 / 536 (0.19%) 1 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 1 / 536 (0.19%) 1 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Angiocardiogram | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 0 / 536 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Blood potassium increased | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 0 / 536 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood pressure decreased | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 7 / 542 (1.29%) | 6 / 536 (1.12%) | |
| occurrences (all) | 8 | 7 | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 0 / 536 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| N-terminal prohormone brain natriuretic peptide increased | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 0 / 536 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Chest injury | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 3 / 536 (0.56%) 3 | |
| Humerus fracture subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Ligament sprain subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Skin laceration subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Toxicity to various agents subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Cardiac disorders | | | |
| Angina unstable subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Arrhythmia subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 1 / 536 (0.19%) 1 | |
| Bradycardia subjects affected / exposed occurrences (all) | 4 / 542 (0.74%) 4 | 2 / 536 (0.37%) 2 | |
| Cardiac failure subjects affected / exposed occurrences (all) | 45 / 542 (8.30%) 51 | 30 / 536 (5.60%) 31 | |
| Cardiac failure acute subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Cardiac failure chronic subjects affected / exposed occurrences (all) | 3 / 542 (0.55%) 3 | 1 / 536 (0.19%) 1 | |

| | | | |
|---|----------------------|----------------------|--|
| Coronary artery disease subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Extrasystoles subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 5 / 536 (0.93%) 5 | |
| Nervous system disorders | | | |
| Burning sensation subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 542 (0.74%) 4 | 0 / 536 (0.00%) 0 | |
| Dizziness exertional subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Dizziness postural subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 1 / 536 (0.19%) 1 | |
| Loss of consciousness subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 0 / 536 (0.00%) 0 | |
| Somnolence | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 1 / 536 (0.19%) 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 0 / 536 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Anaemia of chronic disease | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences (all) | 1 | 1 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 2 / 536 (0.37%) | |
| occurrences (all) | 2 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 1 / 536 (0.19%) | |
| occurrences (all) | 3 | 1 | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 0 / 536 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 0 / 536 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Eructation | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal motility disorder | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemorrhoids | | | |

| | | | |
|--|------------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 0 / 536 (0.00%) 0 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 1 / 536 (0.19%) 1 | |
| Skin ulcer subjects affected / exposed occurrences (all) | 0 / 542 (0.00%) 0 | 1 / 536 (0.19%) 1 | |
| Stasis dermatitis subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 2 / 542 (0.37%) 2 | 0 / 536 (0.00%) 0 | |
| Renal failure subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Renal impairment subjects affected / exposed occurrences (all) | 12 / 542 (2.21%) 14 | 0 / 536 (0.00%) 0 | |
| Urinary retention subjects affected / exposed occurrences (all) | 1 / 542 (0.18%) 1 | 0 / 536 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| Arthritis | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 1 / 536 (0.19%) | |
| occurrences (all) | 2 | 1 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gouty arthritis | | | |
| subjects affected / exposed | 2 / 542 (0.37%) | 1 / 536 (0.19%) | |
| occurrences (all) | 2 | 1 | |
| Hypercreatinaemia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 4 / 542 (0.74%) | 0 / 536 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Corona virus infection | | | |
| subjects affected / exposed | 4 / 542 (0.74%) | 2 / 536 (0.37%) | |
| occurrences (all) | 4 | 2 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Malaria | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 542 (1.48%) | 3 / 536 (0.56%) | |
| occurrences (all) | 8 | 3 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngitis | | | |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 3 / 542 (0.55%) | 5 / 536 (0.93%) | |
| occurrences (all) | 3 | 5 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gout | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|-----------------------------|------------------|-----------------|--|
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 542 (0.00%) | 1 / 536 (0.19%) | |
| occurrences (all) | 0 | 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 17 / 542 (3.14%) | 0 / 536 (0.00%) | |
| occurrences (all) | 18 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 1 / 536 (0.19%) | |
| occurrences (all) | 1 | 1 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 542 (0.18%) | 0 / 536 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 11 June 2019 | After the study started, the protocol was amended to add a patient contact at 180 days for safety. |
| 11 January 2021 | After the study started, the protocol was amended to increase study power by changing the timing of assessment for the primary endpoint from 90 to 180 days and increasing target enrolment from 900 to 1800. |

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 study was terminated on Sept 23, 2022, following the recommendation of the DSMB due to a larger-than-expected difference in risk of the primary endpoint between the groups based on an analysis when 1069 total patients had been randomly assigned.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34529313>

<http://www.ncbi.nlm.nih.gov/pubmed/31423712>

<http://www.ncbi.nlm.nih.gov/pubmed/36356631>