



Clinical trial results:

a Prospective evaluation of natRiuretic pEptide based reFerral of CHF patiEnts in pRimary care - PREFER

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-000473-20 |
| Trial protocol | HR |
| Global end of trial date | 23 March 2018 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 07 April 2019 |
| First version publication date | 07 April 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLCZ696B3402 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02807857 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Study Director, Novartis Pharma, AG, +41 613241111, Novartis.email@novartis.com |
| Scientific contact | Study Director, Novartis Pharma, AG, +41 613241111, Novartis.email@novartis.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 | 23 March 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 23 March 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess if NT-proBNP measurement-guided cardiologist-referral of CHF patients, who were currently judged by their primary care physician as being clinically stable*, leads to optimization of HF treatment, defined as adherence# to level I-A treatment recommendations of the current§ ESC guidelines for the treatment of HF.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 07 July 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Russian Federation: 226 |
| Country: Number of subjects enrolled | Belgium: 201 |
| Country: Number of subjects enrolled | Croatia: 169 |
| Country: Number of subjects enrolled | Slovenia: 122 |
| Country: Number of subjects enrolled | Poland: 120 |
| Country: Number of subjects enrolled | Lithuania: 103 |
| Country: Number of subjects enrolled | Hungary: 94 |
| Country: Number of subjects enrolled | France: 89 |
| Country: Number of subjects enrolled | Spain: 76 |
| Country: Number of subjects enrolled | Norway: 58 |
| Country: Number of subjects enrolled | Cyprus: 36 |
| Country: Number of subjects enrolled | Latvia: 34 |
| Country: Number of subjects enrolled | Malta: 26 |
| Country: Number of subjects enrolled | Estonia: 18 |
| Country: Number of subjects enrolled | Denmark: 19 |
| Country: Number of subjects enrolled | Portugal: 13 |
| Country: Number of subjects enrolled | Israel: 7 |
| Country: Number of subjects enrolled | Italy: 4 |

| | |
|------------------------------------|------|
| Worldwide total number of subjects | 1415 |
| EEA total number of subjects | 1182 |

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) | 482 |
| From 65 to 84 years | 809 |
| 85 years and over | 124 |

Subject disposition

Recruitment

Recruitment details:

The enrolled set consisted of 1415 patients (1431 patients entered the study, of which 16 patients were not included in the analysis due to missing core baseline characteristics, missing informed consent or both). Based on findings from the interim-analysis, Novartis decided to terminate the study prematurely in March 2018.

Pre-assignment

Screening details:

The enrolled set consisted of 1415 patients (1431 patients entered the study, of which 16 patients were not included in the analysis due to missing core baseline characteristics, missing informed consent or both). Based on findings from the interim-analysis, Novartis decided to terminate the study prematurely in March 2018.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Enrolled Set |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-------------------|
| Arm title | Enrolled Patients |
|-----------|-------------------|

Arm description:

Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. Patients who were considered clinically stable and with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set.

| | |
|--|------------------|
| Arm type | Low Intervention |
| Investigational medicinal product name | LCZ696 |
| Investigational medicinal product code | LCZ696 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Not Applicable

| Number of subjects in period 1 | Enrolled Patients |
|--------------------------------------|-------------------|
| Started | 1415 |
| Completed | 864 |
| Not completed | 551 |
| Patients not suitable for follow-up. | 551 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Follow-Up Set |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|-------------------|
| Arm title | Enrolled Patients |
|------------------|-------------------|

Arm description:

Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. Patients who were considered clinically stable and with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set.

| | |
|---|------------------|
| Arm type | Low-Intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Enrolled Patients |
|--------------------------------|-------------------|
| Started | 864 |
| Completed | 680 |
| Not completed | 184 |
| Adverse event, serious fatal | 27 |
| Relocation | 2 |
| Consent withdrawn by subject | 8 |
| Physician decision | 6 |
| Study Terminated By Sponsor | 131 |
| Adverse event, non-fatal | 3 |
| Lost to follow-up | 7 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------|
| Reporting group title | Enrolled Patients |
| Reporting group description: | |
| Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. Patients who were considered clinically stable and with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set. | |

| Reporting group values | Enrolled Patients | Total | |
|---|-------------------|-------|--|
| Number of subjects | 1415 | 1415 | |
| Age, Customized | | | |
| Units: Subjects | | | |
| <65 years | 482 | 482 | |
| \geq 65 years to <75 years | 408 | 408 | |
| \geq 75 years to <85 years | 401 | 401 | |
| \geq 85 years | 124 | 124 | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 69.8 | | |
| standard deviation | \pm 11.6 | - | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 436 | 436 | |
| Male | 979 | 979 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 5 | 5 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 2 | |
| White | 1282 | 1282 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 126 | 126 | |

Subject analysis sets

| | |
|---|--------------------|
| Subject analysis set title | Enrolled Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. | |
| Subject analysis set title | Follow-Up Set |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Patients who were considered clinically stable and with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set. | |

| Reporting group values | Enrolled Set | Follow-Up Set | |
|---|--------------|---------------|--|
| Number of subjects | 1415 | 861 | |
| Age, Customized Units: Subjects | | | |
| <65 years | 275 | 207 | |
| ≥65 years to <75 years | 144 | 264 | |
| ≥75 years to <85 years | 108 | 293 | |
| ≥85 years | 27 | 97 | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 0 | 0 | |
| standard deviation | ± 0 | ± 0 | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 436 | 278 | |
| Male | 979 | 583 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 5 | 4 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 1 | |
| White | 1282 | 772 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 37 | 30 | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Enrolled Patients |
| Reporting group description: Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. Patients who were considered clinically stable an with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set. | |
| Reporting group title | Enrolled Patients |
| Reporting group description: Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. Patients who were considered clinically stable an with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set. | |
| Subject analysis set title | Enrolled Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Adult male and female patients with chronic heart failure with reduced ejection fraction (LVEF \leq 40%) who were managed in a primary care setting in sites across Europe. | |
| Subject analysis set title | Follow-Up Set |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Patients who were considered clinically stable an with NT-proBNP levels > 600 pg/ml were referred to a cardiologist for evaluation and were in the follow-up set. | |

Primary: Number of clinically stable patients whose therapy regimen adheres to ESC guideline recommendations before and after specialist referral

| | |
|---|---|
| End point title | Number of clinically stable patients whose therapy regimen adheres to ESC guideline recommendations before and after specialist referral ^[1] |
| End point description: Assessment of patients' treatment regimen with respect to ESC guideline adherence at baseline (Visit 1) and after referral to a specialist (visit 2) | |
| End point type | Primary |
| End point timeframe: Baseline | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No Statistical Analyses was performed | |

| End point values | Enrolled Set | Follow-Up Set | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Participants | 146 | 75 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Adherence to ESC guideline (Follow-up Set)

| | |
|---|---|
| End point title | Adherence to ESC guideline (Follow-up Set) ^[2] |
| End point description: Adherence to ESC guideline at month 6 | |
| End point type | Primary |
| End point timeframe: Month 6 | |
| Notes: [2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No Statistical Analyses was performed | |

| End point values | Follow-Up Set | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Participants | | | | |
| Patients not adherent at Baseline | 495 | | | |
| Patients adherent at baseline | 15 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Heart Failure

| | |
|--|---------------------------|
| End point title | Duration of Heart Failure |
| End point description: The duration of Heart Failure was collected at Baseline (Visit 1). | |
| End point type | Secondary |
| End point timeframe: Baseline (Visit 1) | |

| End point values | Enrolled Patients | Follow-Up Set | | |
|-----------------------------|-------------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Participants | | | | |
| > 3 years | 896 | 549 | | |
| ≤ 3 years | 517 | 312 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with previously taken and current use of

concomitant compound

| | |
|-----------------|--|
| End point title | Number of patients with previously taken and current use of concomitant compound |
|-----------------|--|

End point description:

Previously taken and current use of concomitant compound was collected at baseline (Visit 1), 6 and 10 months post-baseline.

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

End point timeframe:

Baseline (Visit 1), 6 months

| End point values | Enrolled Set | Follow-Up Set | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Participants | | | | |
| Diuretics – without mineral corticoid antagonists | 934 | 625 | | |
| Beta blocking agents | 981 | 602 | | |
| Agents acting on the renin-angiotensin system | 834 | 491 | | |
| Diuretics – mineral corticoid antagonists | 664 | 416 | | |
| Antithrombotic agents | 401 | 256 | | |
| Cardiac therapy | 365 | 238 | | |
| Lipid modifying agents | 163 | 96 | | |
| Mineral supplements | 110 | 69 | | |
| Calcium channel blockers | 65 | 39 | | |
| Antihypertensives | 15 | 7 | | |
| Drugs for acid related disorders | 9 | 7 | | |
| All other therapeutic products | 4 | 4 | | |
| Antianemic preparations | 3 | 2 | | |
| Ophthalmologicals | 3 | 3 | | |
| Drugs used in diabetes | 2 | 0 | | |
| Analgesics | 1 | 0 | | |
| Antiepileptics | 1 | 1 | | |
| Peripheral vasodilators | 1 | 0 | | |
| Psychoanaleptics | 1 | 1 | | |
| Unspecified herbal and traditional medicine | 1 | 0 | | |
| Urologicals | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of clinically stable patients for whom the cardiologist and/or primary care physician optimizes treatment post referral, stratified according to key baseline characteristics

| | |
|-----------------|---|
| End point title | Percentages of clinically stable patients for whom the cardiologist and/or primary care physician optimizes treatment |
|-----------------|---|

End point description:

For patients who enter the prospective period of the study the post-referral treatment choice of cardiologists and/or primary care physicians was documented; for patients, for whom the cardiologist and/or primary care physician chose to prescribe a novel Heart Failure treatment, the treatment was assessed, if it fulfills the definition of adherence to European Society of Cardiology (ESC) guideline recommendation. The proportion of patients for whom an ESC guideline adherent treatment was de novo prescribed was assessed stratified according to different parameters.

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

End point timeframe:

6 and 10 months

| End point values | Follow-Up Set | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Percentage of Patients | | | | |
| number (not applicable) | | | | |
| Cardiologist`s advice-No change | 45.1 | | | |
| Cardiologist`s advice-Treatment intensification | 30.7 | | | |
| Cardiologist`s advice-Treatment reduction | 6.3 | | | |
| Cardiologist`s advice-Treatment adaption | 17.9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with different NT-proBNP level categories

| | |
|-----------------|--|
| End point title | Number of patients with different NT-proBNP level categories |
|-----------------|--|

End point description:

NT-proBNP levels (pg/ml) was measured at baseline in all consecutive patients who satisfy the inclusion and exclusion criteria. Measurements were performed on-site by means of a handheld device provided for the purposes of the study. NT-proBNP level categories could be 600 -799 pg/ml, 800 – 999 pg/ml, 1000 – 1200 pg/ml, > 1200 pg/ml).

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

End point timeframe:

One measurement in all consecutive patients at baseline (Visit 1)

| End point values | Enrolled Set | Follow-Up Set | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Participants | | | | |
| <600 pg/ml | 495 | 0 | | |
| ≥ 600 pg/ml to <800 pg/ml | 135 | 130 | | |

| | | | | |
|-----------------------------|-----|-----|--|--|
| ≥ 800 pg/ml to <1000 pg/ml | 97 | 93 | | |
| ≥ 1000 pg/ml to <1200 pg/ml | 80 | 75 | | |
| ≥ 1200 pg/ml to <1400 pg/ml | 48 | 46 | | |
| ≥ 1400 pg/ml to <1600 pg/ml | 32 | 24 | | |
| ≥ 1600 pg/ml to <1800 pg/ml | 33 | 33 | | |
| ≥ 1800 pg/ml to <2000 pg/ml | 30 | 29 | | |
| ≥ 2000 pg/ml | 465 | 431 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of clinically stable patients

| | |
|---|---|
| End point title | Percentages of clinically stable patients |
| End point description: Clinically stable patients in this study were defined as those patients for whom the primary care physician did not see a necessity (based on signs and symptoms of HF) to change the current pharmacological and/or device treatment of HF and who were on stable pharmacological and/or device treatment for HF for at least 3 months prior to inclusion. | |
| End point type | Secondary |
| End point timeframe: Baseline (Visit 1) | |

| | | | | |
|---|----------------------|--|--|--|
| End point values | Enrolled Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 1415 | | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Patients clinically stable | 96.9 | | | |
| Patients not clinically stable | 3.1 | | | |
| Patients suitable for prospective period of study | 63.2 | | | |
| Patients not suitable for prospective period | 36.8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients by cardiologist prescription practice per country/region

| | |
|---|---|
| End point title | Number of patients by cardiologist prescription practice per country/region |
| End point description: The cardiologists' suggestions for pharmacological and/or device therapy for the treatment of clinically stable CHF patients was documented and assessed by means of descriptive statistical measures | |

stratified by country/region 6 months after baseline.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| | | | | |
|-------------------------------|----------------------|--|--|--|
| End point values | Follow-Up Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Number of Participants | | | | |
| Western EU | 198 | | | |
| Eastern EU | 525 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change of NT-proBNP levels in clinically stable CHF patients with and without treatment optimization 10 months after baseline

| | |
|-----------------|---|
| End point title | Change of NT-proBNP levels in clinically stable CHF patients with and without treatment optimization 10 months after baseline |
|-----------------|---|

End point description:

At 10 months after baseline (end of study) NT-proBNP was assessed in clinically stable CHF patients with baseline NT-proBNP levels ≥ 600 pg/ml. Thus, for those patients two NT-proBNP measurements were available: at baseline and 10 months later. The individual change of NT-proBNP between both time points were assessed in accordance to the patients' treatment history during the study, i.e. baseline Heart Failure treatment and therapeutic decision taken 6 months after baseline.

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Visit 1) and 10 months | |

| | | | | |
|--|----------------------|--|--|--|
| End point values | Follow-Up Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Count of Participants | | | | |
| arithmetic mean (standard deviation) | | | | |
| NT-proBNP [pg/ml] at Visit 1 (Baseline) | 2753 (\pm 2530) | | | |
| NT-proBNP [pg/ml] at Visit 3 (10 months) | 2245 (\pm 2303) | | | |
| Absolute change in NT-proBNP (V3-V1) | -504 (\pm 2607) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change of EQ-5D total and individual sub-scores between baseline and 6 months later, between baseline and 10 months later

| | |
|-----------------|---|
| End point title | Change of EQ-5D total and individual sub-scores between baseline and 6 months later, between baseline and 10 months later |
|-----------------|---|

End point description:

At baseline (all patients) and at Visit 2 and Visit 3 (only patients who had entered the prospective period of the study, i.e. clinically stable patients with a NT-proBNP level \geq 600 pg/ml) were asked to fill out the EuroQol 5D (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ) – two quality of life (QoL) questionnaires validated for HF.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| End point values | Follow-Up Set | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Count of Participants | | | | |
| arithmetic mean (standard deviation) | | | | |
| EQ5D Utility index - Visit 1 | 0.74 (\pm 0.23) | | | |
| EQ5D Utility index - Visit 2 | 0.75 (\pm 0.21) | | | |
| EQ5D Utility index absolute change (V2-V1) | 0.02 (\pm 0.13) | | | |
| EQ5D Utility index - Visit 3 | 0.75 (\pm 0.22) | | | |
| EQ5D Utility index absolute change (V3-V1) | 0.01 (\pm 0.17) | | | |
| EQ5D Utility index absolute change (V3-V2) | -0.00 (\pm 0.14) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in KCCQ total and individual sub-scores between baseline and 6 months later, between and 10 months later

| | |
|-----------------|---|
| End point title | Change in KCCQ total and individual sub-scores between baseline and 6 months later, between and 10 months later |
|-----------------|---|

End point description:

At baseline (all patients) and at Visit 2 and Visit 3 (only patients who had entered the prospective period of the study, i.e. clinically stable patients with a NT-proBNP level \geq 600 pg/ml) were asked to fill out the EuroQol 5D (EQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ) – two quality of life (QoL) questionnaires validated for Heart Failure.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| End point values | Follow-Up Set | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Count of Participants | | | | |
| arithmetic mean (standard deviation) | | | | |
| KCCQ Overall Summary Score - Visit 1 | 64.1 (± 23.3) | | | |
| KCCQ Overall Summary Score - Visit 2 | 64.9 (± 22.9) | | | |
| KCCQ Overall Summary Score absolute change (V2-V1) | 1.0 (± 12.0) | | | |
| KCCQ Overall Summary Score - Visit 3 | 65.1 (± 22.8) | | | |
| KCCQ Overall Summary Score absolute change (V3-V2) | 0.3 (± 12.1) | | | |
| KCCQ Overall Summary Score absolute change (V3-V1) | 1.7 (± 14.1) | | | |
| KCCQ Clinical Summary Score - Visit 1 | 65.6 (± 22.7) | | | |
| KCCQ Clinical Summary Score - Visit 2 | 66.1 (± 22.4) | | | |
| KCCQ Summary Score absolute change (V2-V1) | 0.9 (± 11.8) | | | |
| KCCQ Clinical Summary Score - Visit 3 | 65.8 (± 22.1) | | | |
| KCCQ Summary Score absolute change (V3-V2) | 0.1 (± 12.4) | | | |
| KCCQ Summary Score absolute change (V3-V1) | 1.2 (± 14.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients in different living conditions

| | |
|---|---|
| End point title | Number of patients in different living conditions |
| End point description: | |
| Living conditions were collected at Baseline (Visit 1). | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Visit 1) | |

| End point values | Enrolled Set | Follow-Up Set | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Living independently in household (alone) | 313 | 204 | | |
| Living with spouse or significant other | 817 | 481 | | |

| | | | | |
|--|-----|-----|--|--|
| Living in residence with other family member | 264 | 159 | | |
| Living in a long term care facility | 20 | 16 | | |
| Transient housing | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients in different employment status

| | |
|--|---|
| End point title | Number of patients in different employment status |
| End point description: Employment status was collected at Baseline (Visit 1). | |
| End point type | Secondary |
| End point timeframe: Baseline (Visit 1) | |

| End point values | Enrolled Set | Follow-Up Set | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Student | 0 | 0 | | |
| Employed (part-time) | 49 | 28 | | |
| Employed (full-time) | 144 | 51 | | |
| Homemaker | 26 | 15 | | |
| Retired | 1034 | 680 | | |
| Unemployed | 85 | 43 | | |
| Sustained Sick Leave | 73 | 40 | | |
| Missing | 4 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with smoking status

| | |
|---|--|
| End point title | Number of patients with smoking status |
| End point description: Smoking status was collected at baseline (visit 1). | |
| End point type | Secondary |
| End point timeframe: Baseline (Visit 1) | |

| End point values | Enrolled Set | Follow-Up Set | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Never | 779 | 500 | | |
| Current | 205 | 113 | | |
| Former | 427 | 246 | | |
| Missing | 4 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients from different geographical regions

| | |
|--|--|
| End point title | Number of patients from different geographical regions |
| End point description: Geographic regions were collected at Baseline (Visit 1). | |
| End point type | Secondary |
| End point timeframe: Baseline (visit 1) | |

| End point values | Enrolled Set | Follow-Up Set | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| RUS | 226 | 173 | | |
| BEL | 201 | 114 | | |
| HRV | 169 | 95 | | |
| SVN | 122 | 72 | | |
| POL | 120 | 74 | | |
| LTU | 103 | 65 | | |
| HUN | 94 | 58 | | |
| FRA | 89 | 54 | | |
| ESP | 76 | 30 | | |
| NOR | 58 | 33 | | |
| CYP | 36 | 20 | | |
| LVA | 34 | 22 | | |
| MLT | 26 | 17 | | |
| EST | 18 | 16 | | |
| DNK | 19 | 4 | | |
| PRT | 13 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with health insurance status

| | |
|-----------------|---|
| End point title | Number of patients with health insurance status |
|-----------------|---|

End point description:

Health insurance status was collected at Baseline (Visit 1).

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

End point timeframe:

Baseline (Visit 1)

| End point values | Enrolled Set | Follow-Up Set | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Statutory Health Insurance | 1168 | 712 | | |
| Private Health Insurance | 29 | 22 | | |
| Combined statutory and private health insurance | 171 | 98 | | |
| None | 47 | 29 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients at different educational level

| | |
|-----------------|---|
| End point title | Number of patients at different educational level |
|-----------------|---|

End point description:

Educational level was collected at Baseline (Visit 1).

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

End point timeframe:

Baseline (Visit 1)

| End point values | Enrolled Set | Follow-Up Set | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Primary Education | 396 | 248 | | |
| Secondary Education | 730 | 421 | | |
| University | 257 | 173 | | |
| None | 30 | 17 | | |
| Missing | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients per primary etiology of Heart Failure

| | |
|------------------------|--|
| End point title | Number of patients per primary etiology of Heart Failure |
| End point description: | The primary etiology of Heart Failure was collected at Baseline (Visit 1). |
| End point type | Secondary |
| End point timeframe: | Baseline (Visit 1) |

| End point values | Enrolled Set | Follow-Up Set | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Primary Etiology- Ischemic | 860 | 541 | | |
| Primary Etiology-Non-Ischemic | 553 | 320 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of heart failure (HF)-related hospitalizations in the previous 12 months prior to baseline, and during the study

| | |
|------------------------|--|
| End point title | Number of heart failure (HF)-related hospitalizations in the previous 12 months prior to baseline, and during the study |
| End point description: | HF-related hospitalizations was collected in the previous 12 months prior to baseline at baseline visit, at 6 and 10 months post-baseline. |
| End point type | Secondary |
| End point timeframe: | Baseline (Visit 1), 6 months, 10 months |

| End point values | Enrolled Set | Follow-Up Set | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Number of Participants | | | | |
| Visit 1- Up to Baseline | 383 | 262 | | |
| Visit 2-6 months | 0 | 18 | | |
| Visit 3-10 months | 0 | 22 | | |
| Missing | 0 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with cardiovascular and non-cardiovascular co-morbidities

| | |
|-----------------|--|
| End point title | Percentage of patients with cardiovascular and non-cardiovascular co-morbidities |
|-----------------|--|

End point description:

Cardiovascular and non-cardiovascular co-morbidities was collected at baseline (Visit 1), 6 and 10 months post-baseline.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| End point values | Enrolled Set | Follow-Up Set | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1415 | 861 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Hypertension | 74.2 | 75.8 | | |
| Dyslipidemia | 61.6 | 58.8 | | |
| History of myocardial infarction | 43.9 | 44.4 | | |
| Atrial fibrillation | 40.8 | 52.3 | | |
| Obesity | 36.1 | 30.8 | | |
| Stable angina pectoris | 31.4 | 33.8 | | |
| Diabetes mellitus type 2 | 29.9 | 31.5 | | |
| Other Comorbidities | 13.0 | 14.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean dose of previously taken and current use of concomitant compound

| | |
|-----------------|---|
| End point title | Mean dose of previously taken and current use of concomitant compound |
|-----------------|---|

End point description:

The mean dose of previously taken and current use of concomitant compound, was collected at Baseline (Visit 1), 6 and 10 months post-baseline.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| | | | | |
|--------------------------------------|----------------------|--|--|--|
| End point values | Follow-Up Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of device type

| | |
|-----------------|-----------------------|
| End point title | Number of device type |
|-----------------|-----------------------|

End point description:

The numbers of device type was collected at Baseline (Visit 1), at 6 and 10 months post-baseline.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| | | | | |
|---|----------------------|--|--|--|
| End point values | Follow-Up Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Number of Participants | | | | |
| One ACEi or one ARB and one beta-blocker(V1) | 178 | | | |
| Exactly one beta-blocker and one MRA(V1) | 166 | | | |
| Exactly one ACEi or one ARB and one MRA(V1) | 165 | | | |
| One ACEi or (1)ARB & (1)MRA & (1)beta-blocker(V1) | 82 | | | |
| Exactly one beta-blocker and ARNi(V1) | 13 | | | |

| | | | | |
|---|-----|--|--|--|
| Exactly one MRA and ARNi(V1) | 20 | | | |
| Exactly one MRA and one beta-blocker and ARNi(V1) | 9 | | | |
| One ACEi or one ARB and one beta-blocker(V2) | 156 | | | |
| Exactly one beta-blocker and one MRA(V2) | 160 | | | |
| Exactly one ACEi or one ARB and one MRA(V2) | 177 | | | |
| One ACEi or (1)ARB & (1)MRA & (1)beta-blocker(V2) | 91 | | | |
| Exactly one beta-blocker and ARNi(V2) | 17 | | | |
| Exactly one MRA and ARNi(V2) | 23 | | | |
| Exactly one MRA and one beta-blocker and ARNi(V2) | 10 | | | |
| One ACEi or one ARB and one beta-blocker(V3) | 120 | | | |
| Exactly one beta-blocker and one MRA(V3) | 130 | | | |
| Exactly one ACEi or one ARB and one MRA(V3) | 143 | | | |
| One ACEi or (1)ARB & (1)MRA & (1)beta-blocker(V3) | 77 | | | |
| Exactly one beta-blocker and ARNi(V3) | 11 | | | |
| Exactly one MRA and ARNi(V3) | 17 | | | |
| Exactly one MRA and one beta-blocker and ARNi(V3) | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of treatment with device type

| | |
|---|--|
| End point title | Duration of treatment with device type |
| End point description: | |
| The duration of treatment with device type was collected at baseline (Visit 1), at 6 and 10 months post-baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Visit 1), 6 months, 10 months | |

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | Follow-Up Set | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Years | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of previously taken and currently use of concomitant compound

| | |
|-----------------|--|
| End point title | Duration of previously taken and currently use of concomitant compound |
|-----------------|--|

End point description:

Duration of previously taken and current use of concomitant compound, was collected at Baseline (Visit 1), 6 and 10 months post-baseline.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| End point values | Follow-Up Set | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Number of Participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients by primary care physicians' prescription practice per country/region

| | |
|-----------------|---|
| End point title | Number of patients by primary care physicians' prescription practice per country/region |
|-----------------|---|

End point description:

For clinically stable CHF patients, the primary care physicians' prescription of pharmacological and device treatment for HF was documented prior to (at baseline) and post cardiologist-referral (6 and 10 months after baseline). At the post-referral visit the degree of implementation of cardiologist-recommendations and the medical decision making (e.g. reasons for non-implementation) was documented.

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

End point timeframe:

Baseline (Visit 1), 6 months, 10 months

| End point values | Follow-Up Set | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 861 | | | |
| Units: Number of Participants | 0 | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from FPFV to LPLV up to 2 years.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Enrolled |
|-----------------------|----------|

Reporting group description:

Enrolled

| | |
|-----------------------|-----------|
| Reporting group title | Follow-Up |
|-----------------------|-----------|

Reporting group description:

Follow-Up

| Serious adverse events | Enrolled | Follow-Up | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 117 / 1415 (8.27%) | 114 / 861 (13.24%) | |
| number of deaths (all causes) | 32 | 30 | |
| number of deaths resulting from adverse events | 4 | 4 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Brain neoplasm | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroendocrine tumour | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Aortic valve repair | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac ablation | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac pacemaker insertion | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac resynchronisation therapy | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardioversion | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 3 | 1 / 2 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue inflammation | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Sudden death | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| Homicide | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterovaginal prolapse | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 4 / 1415 (0.28%) | 3 / 861 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthopnoea | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electric shock | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 9 / 1415 (0.64%) | 9 / 861 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 9 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 29 / 1415 (2.05%) | 27 / 861 (3.14%) | |
| occurrences causally related to treatment / all | 2 / 33 | 2 / 31 | |
| deaths causally related to treatment / all | 1 / 9 | 1 / 8 | |
| Cardiac failure acute | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 4 / 1415 (0.28%) | 4 / 861 (0.46%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 4 / 1415 (0.28%) | 4 / 861 (0.46%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Syncope | | | |
| subjects affected / exposed | 5 / 1415 (0.35%) | 5 / 861 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Short-bowel syndrome | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Ischaemic skin ulcer | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Intestinal gangrene | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orchitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 9 / 1415 (0.64%) | 9 / 861 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 10 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Enrolled | Follow-Up | |
|---|------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 187 / 1415 (13.22%) | 181 / 861 (21.02%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 1415 (0.42%) | 3 / 861 (0.35%) | |
| occurrences (all) | 6 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 1415 (0.42%) | 6 / 861 (0.70%) | |
| occurrences (all) | 6 | 6 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Venous thrombosis | | | |

| | | | |
|---|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Surgical and medical procedures | | | |
| Cataract operation | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 4 | 4 | |
| Coronary angioplasty | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Dental operation | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Intraocular lens implant | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 2 | 2 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 7 / 1415 (0.49%) | 7 / 861 (0.81%) | |
| occurrences (all) | 7 | 7 | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 1415 (0.64%) | 9 / 861 (1.05%) | |
| occurrences (all) | 9 | 9 | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 1415 (0.57%) | 8 / 861 (0.93%) | |
| occurrences (all) | 9 | 9 | |
| Pyrexia | | | |

| | | | |
|---|------------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Thirst subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Bronchiectasis subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Catarrh subjects affected / exposed occurrences (all) | 2 / 1415 (0.14%) 2 | 2 / 861 (0.23%) 2 | |
| Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) | 5 / 1415 (0.35%) 5 | 5 / 861 (0.58%) 5 | |
| Chronic respiratory failure subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Cough subjects affected / exposed occurrences (all) | 6 / 1415 (0.42%) 6 | 6 / 861 (0.70%) 6 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 1415 (0.14%) 2 | 2 / 861 (0.23%) 2 | |
| Dyspnoea at rest subjects affected / exposed occurrences (all) | 2 / 1415 (0.14%) 3 | 2 / 861 (0.23%) 3 | |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 9 / 1415 (0.64%) 10 | 9 / 861 (1.05%) 10 | |
| Dyspnoea paroxysmal nocturnal | | | |

| | | | |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Nocturnal dyspnoea | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Orthopnoea | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Productive cough | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Rales | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Psychiatric disorders | | | |

| | | | |
|--|-------------------|------------------|--|
| Anxiety | | | |
| subjects affected / exposed | 12 / 1415 (0.85%) | 12 / 861 (1.39%) | |
| occurrences (all) | 12 | 12 | |
| Anxiety disorder | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Depression | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Nightmare | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Blood creatinine abnormal | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 0 / 861 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Blood iron decreased | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Blood pressure abnormal | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Blood pressure diastolic increased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Haemoglobin increased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| N-terminal prohormone brain natriuretic peptide increased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Prostatic specific antigen increased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Vitamin B12 decreased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Epicondylitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Ligament sprain | | | |

| | | | |
|---|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Limb injury subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Rib fracture subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Cardiac disorders Arteriosclerosis coronary artery subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 5 / 1415 (0.35%) 5 | 5 / 861 (0.58%) 5 | |
| Cardiac failure subjects affected / exposed occurrences (all) | 5 / 1415 (0.35%) 5 | 5 / 861 (0.58%) 5 | |
| Cardio-respiratory arrest subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Hypertensive cardiomyopathy subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Palpitations subjects affected / exposed occurrences (all) | 3 / 1415 (0.21%) 3 | 3 / 861 (0.35%) 3 | |
| Tachyarrhythmia subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Nervous system disorders Carotid artery stenosis | | | |

| | | | |
|--------------------------------------|-------------------|------------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 1415 (0.35%) | 5 / 861 (0.58%) | |
| occurrences (all) | 5 | 5 | |
| Headache | | | |
| subjects affected / exposed | 15 / 1415 (1.06%) | 15 / 861 (1.74%) | |
| occurrences (all) | 15 | 15 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Leukoencephalopathy | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 1415 (0.42%) | 6 / 861 (0.70%) | |
| occurrences (all) | 7 | 7 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Vertigo | | | |
| subjects affected / exposed | 6 / 1415 (0.42%) | 6 / 861 (0.70%) | |
| occurrences (all) | 6 | 6 | |
| Eye disorders | | | |

| | | | |
|--|-----------------------|----------------------|--|
| Accommodation disorder subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Cataract subjects affected / exposed occurrences (all) | 4 / 1415 (0.28%) 5 | 4 / 861 (0.46%) 5 | |
| Diplopia subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Sudden visual loss subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 1415 (0.21%) 3 | 3 / 861 (0.35%) 3 | |
| Abdominal wall haematoma subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Anal haemorrhage subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Cheilitis subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 1415 (0.42%) 6 | 6 / 861 (0.70%) 6 | |
| Dyspepsia | | | |

| | | |
|--------------------------------------|------------------|-----------------|
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) |
| occurrences (all) | 2 | 2 |
| Dry mouth | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Enterocolitis | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Functional gastrointestinal disorder | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Gastric ulcer | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Gastritis | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) |
| occurrences (all) | 2 | 2 |
| Gastroduodenitis | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Gastrointestinal angiodysplasia | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Haematochezia | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) |
| occurrences (all) | 2 | 2 |
| Inguinal hernia | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Melaena | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Nausea | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) |
| occurrences (all) | 2 | 2 |
| Vomiting | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Dermatitis | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Skin ulcer | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Urticaria | | | |

| | | | |
|--|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Nephropathy | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Nocturia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Pollakiuria | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Renal failure | | | |
| subjects affected / exposed | 4 / 1415 (0.28%) | 4 / 861 (0.46%) | |
| occurrences (all) | 4 | 4 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Back pain | | | |

| | | |
|---------------------------------|------------------|-----------------|
| subjects affected / exposed | 8 / 1415 (0.57%) | 8 / 861 (0.93%) |
| occurrences (all) | 8 | 8 |
| Cervical spinal stenosis | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Gouty arthritis | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) |
| occurrences (all) | 3 | 3 |
| Joint range of motion decreased | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Muscle spasms | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Muscular weakness | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Musculoskeletal pain | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 0 / 861 (0.00%) |
| occurrences (all) | 1 | 0 |
| Neck pain | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Osteitis | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Osteoarthritis | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Osteoporosis | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) |
| occurrences (all) | 2 | 2 |
| Rotator cuff syndrome | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) |
| occurrences (all) | 1 | 1 |
| Spinal pain | | |

| | | | |
|----------------------------------|-------------------|------------------|--|
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Temporomandibular joint syndrome | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Tendon disorder | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Tendonitis | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Torticollis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 10 / 1415 (0.71%) | 10 / 861 (1.16%) | |
| occurrences (all) | 11 | 11 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Gingivitis | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |

| | | |
|---|-----------------------|----------------------|
| Lower respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 1415 (0.14%) 2 | 2 / 861 (0.23%) 2 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 1415 (0.28%) 4 | 4 / 861 (0.46%) 4 |
| Onychomycosis subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 |
| Otitis media acute subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 |
| Pharyngitis subjects affected / exposed occurrences (all) | 2 / 1415 (0.14%) 2 | 2 / 861 (0.23%) 2 |
| Pulpitis dental subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 |
| Pyuria subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 1415 (0.14%) 2 | 2 / 861 (0.23%) 2 |
| Skin infection subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 |
| Tracheobronchitis subjects affected / exposed occurrences (all) | 1 / 1415 (0.07%) 1 | 1 / 861 (0.12%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 1415 (0.21%) 3 | 2 / 861 (0.23%) 2 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 9 / 1415 (0.64%) 9 | 9 / 861 (1.05%) 9 |

| | | | |
|------------------------------------|------------------|-----------------|--|
| Viral infection | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Viral sinusitis | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Gout | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 1415 (0.07%) | 1 / 861 (0.12%) | |
| occurrences (all) | 1 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |
| Obesity | | | |
| subjects affected / exposed | 3 / 1415 (0.21%) | 3 / 861 (0.35%) | |
| occurrences (all) | 3 | 3 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 1415 (0.14%) | 2 / 861 (0.23%) | |
| occurrences (all) | 2 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

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| The recruitment was to be regarded as completed once approx. 2400 patients had entered the prospective period. However it was decided by Novartis to terminate the study prematurely, in March 2018. |
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Notes: