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 ≤ 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.

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 ≤ 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.

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 ≤ 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 values	Enrolled Patients	Total	
Number of subjects	1415	1415	
Age, Customized Units: Subjects			
<65 years	482	482	
≥65 years to <75 years	408	408	
≥75 years to <85 years	401	401	
≥85 years	124	124	
Age Continuous Units: Years			
arithmetic mean	69.8		
standard deviation	± 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 ≤ 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.	

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 ≤ 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 ≤ 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 ≤ 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

	post referral, stratified according to key baseline characteristics

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 (± 2530)			
NT-proBNP [pg/ml] at Visit 3 (10 months)	2245 (± 2303)			
Absolute change in NT-proBNP (V3-V1)	-504 (± 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 ≥ 600 pg/ml) were be 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 (± 0.23)			
EQ5D Utility index - Visit 2	0.75 (± 0.21)			
EQ5D Utility index absolute change (V2-V1)	0.02 (± 0.13)			
EQ5D Utility index - Visit 3	0.75 (± 0.22)			
EQ5D Utility index absolute change (V3-V1)	0.01 (± 0.17)			
EQ5D Utility index absolute change (V3-V2)	-0.00 (± 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 ≥ 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 (± 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

No statistical analyses for this end point

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	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	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	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Thirst			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Bronchiectasis			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Catarrh			
subjects affected / exposed	2 / 1415 (0.14%)	2 / 861 (0.23%)	
occurrences (all)	2	2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 1415 (0.35%)	5 / 861 (0.58%)	
occurrences (all)	5	5	
Chronic respiratory failure			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	6 / 1415 (0.42%)	6 / 861 (0.70%)	
occurrences (all)	6	6	
Dyspnoea			
subjects affected / exposed	2 / 1415 (0.14%)	2 / 861 (0.23%)	
occurrences (all)	2	2	
Dyspnoea at rest			
subjects affected / exposed	2 / 1415 (0.14%)	2 / 861 (0.23%)	
occurrences (all)	3	3	
Dyspnoea exertional			
subjects affected / exposed	9 / 1415 (0.64%)	9 / 861 (1.05%)	
occurrences (all)	10	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	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Limb injury			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Rib fracture			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Atrial fibrillation			
subjects affected / exposed	5 / 1415 (0.35%)	5 / 861 (0.58%)	
occurrences (all)	5	5	
Cardiac failure			
subjects affected / exposed	5 / 1415 (0.35%)	5 / 861 (0.58%)	
occurrences (all)	5	5	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Hypertensive cardiomyopathy			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	3 / 1415 (0.21%)	3 / 861 (0.35%)	
occurrences (all)	3	3	
Tachyarrhythmia			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Tachycardia			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	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	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Cataract			
subjects affected / exposed	4 / 1415 (0.28%)	4 / 861 (0.46%)	
occurrences (all)	5	5	
Diplopia			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Sudden visual loss			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Visual acuity reduced			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	3 / 1415 (0.21%)	3 / 861 (0.35%)	
occurrences (all)	3	3	
Abdominal wall haematoma			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Anal haemorrhage			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Cheilitis			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	6 / 1415 (0.42%)	6 / 861 (0.70%)	
occurrences (all)	6	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	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	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	2 / 1415 (0.14%)	2 / 861 (0.23%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	4 / 1415 (0.28%)	4 / 861 (0.46%)	
occurrences (all)	4	4	
Onychomycosis			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Otitis media acute			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	2 / 1415 (0.14%)	2 / 861 (0.23%)	
occurrences (all)	2	2	
Pulpitis dental			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Pyuria			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	2 / 1415 (0.14%)	2 / 861 (0.23%)	
occurrences (all)	2	2	
Skin infection			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Tracheobronchitis			
subjects affected / exposed	1 / 1415 (0.07%)	1 / 861 (0.12%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 1415 (0.21%)	2 / 861 (0.23%)	
occurrences (all)	3	2	
Urinary tract infection			
subjects affected / exposed	9 / 1415 (0.64%)	9 / 861 (1.05%)	
occurrences (all)	9	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

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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 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.

Notes: