Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate Cardiovascular Outcomes of TAK-875, 50 mg in Addition to Standard of Care in Subjects with Type 2 Diabetes and with Cardiovascular Disease or Multiple Risk Factors for Cardiovascular Events

Summary

EudraCT number	2011-001732-37
Trial protocol	HU CZ SK DE EE LT LV GB IT BG PL
Global end of trial date	05 May 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	TAK-875_306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01609582
WHO universal trial number (UTN)	U1111-1129-7824

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Program Manager, Takeda Global Research & Development Centre (Europe) Ltd., 0044 0203116 8000, clinicaloperations@tgrd.com
Scientific contact	Program Manager, Takeda Global Research & Development Centre (Europe) Ltd., 0044 0203116 8000, clinicaloperations@tgrd.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	19 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that no excess risk of cardiovascular (CV) composite events exists following treatment with
TAK-875 (fasiglifam) compared with placebo when given in combination with Standard of Care in subjects with type 2 diabetes mellitus (T2DM) and clinically evident CV disease or multiple risk factors for CV events. For purposes of this study, the primary major adverse cardiovascular events (MACE) composite comprises CV death, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for unstable angina (with or without revascularization).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 62
Country: Number of subjects enrolled	Poland: 236
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Bulgaria: 43
Country: Number of subjects enrolled	Czech Republic: 112
Country: Number of subjects enrolled	Estonia: 24
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	Hungary: 146
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Latvia: 22
Country: Number of subjects enrolled	Lithuania: 30
Country: Number of subjects enrolled	Argentina: 242
Country: Number of subjects enrolled	Australia: 69
Country: Number of subjects enrolled	Canada: 211
Country: Number of subjects enrolled	Croatia: 33
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hong Kong: 58
Country: Number of subjects enrolled	Israel: 51

Country: Number of subjects enrolled	Korea, Republic of: 56
Country: Number of subjects enrolled	Malaysia: 61
Country: Number of subjects enrolled	Mexico: 52
Country: Number of subjects enrolled	New Zealand: 40
Country: Number of subjects enrolled	Peru: 35
Country: Number of subjects enrolled	Philippines: 49
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 48
Country: Number of subjects enrolled	South Africa: 20
Country: Number of subjects enrolled	Taiwan: 62
Country: Number of subjects enrolled	Thailand: 61
Country: Number of subjects enrolled	Ukraine: 152
Country: Number of subjects enrolled	United States: 1118
Worldwide total number of subjects	3207
EEA total number of subjects	822

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)	1645
From 65 to 84 years	1543
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 469 investigative sites in 31 countries; 192 sites in North America, 175 in the Europe, Middle East, and Africa (EMEA) region (including Russia, Ukraine, Israel, and South Africa), 65 in the Asia Pacific region, and 37 in Latin/South America from 01 June 2012 to 05 May 2014.

Pre-assignment

Screening details:

Subjects with a historical diagnosis of T2DM and clinically-evident CV disease or multiple risk factors for CV events who were inadequately controlled while receiving the standard of care were enrolled in 1 of 2 treatment groups: placebo; fasiglifam 50 milligram (mg).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Fasiglifam placebo-matching tablet, orally, once daily for up to 588 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fasiglifam placebo-matching tablet, orally, once daily for up to 588 days.

Arm title	Fasiglifam 50 mg

Arm description:

Fasiglifam 50 mg, tablet, orally, once daily for up to 582 days.

Arm type	Experimental
Investigational medicinal product name	Fasiglifam
Investigational medicinal product code	
Other name	TAK-875
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fasiglifam 50 mg, tablet, orally, once daily for up to 582 days.

Number of subjects in period 1	Placebo	Fasiglifam 50 mg
Started	1603	1604
Treated	1603	1601
Completed	0	0
Not completed	1603	1604
Randomized, but not treated	-	3
Other	9	10
Adverse event	20	18
Study terminated by sponsor	1543	1548
Lost to follow-up	10	10
Withdrawal by subject	21	15

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Fasiglifam placebo-matching tablet, orally, once daily for up to 588 days.	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
Fasiglifam 50 mg, tablet, orally, once daily for up to 582 days.	

Reporting group values	Placebo	Fasiglifam 50 mg	Total
Number of subjects	1603	1604	3207
Age categorical Units: Subjects			
Less than (<) 65 years	794	851	1645
Greater than or equal to (>=) 65 years	809	753	1562
Age continuous Units: years			
arithmetic mean	63.9	63.4	
standard deviation	± 9.03	± 9.2	-
Gender categorical Units: Subjects			
Female	543	563	1106
Male	1060	1041	2101
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	150	119	269
Not Hispanic or Latino	446	477	923
Unknown or Not Reported	1007	1008	2015
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	47	41	88
Asian	199	205	404
Native Hawaiian or Other Pacific Islander	6	7	13
Black or African American	79	95	174
White	1265	1246	2511
Multiracial/More than 1 race	7	10	17
Glycosylated Hemoglobin (HbA1c) Category Units: Subjects			
<8.5 percent (%)	988	936	1924
>=8.5%	615	668	1283
Smoking Classification Units: Subjects			
Never smoked	667	668	1335
Current smoker	330	328	658
Ex-smoker	606	608	1214
Region of Enrollment			

Units: Subjects			
Argentina	121	121	242
Australia	34	35	69
Bulgaria	21	22	43
Canada	104	107	211
Croatia	16	17	33
Czech Republic	56	56	112
Estonia	13	11	24
France	3	4	7
Germany	30	30	60
Hong Kong	29	29	58
Hungary	74	72	146
Israel	25	26	51
Italy	3	3	6
Korea, Republic of	29	27	56
Latvia	11	11	22
Lithuania	15	15	30
Malaysia	30	31	61
Mexico	26	26	52
New Zealand	20	20	40
Peru	18	17	35
Philippines	25	24	49
Poland	118	118	236
Romania	5	4	9
Russian Federation	25	23	48
Slovakia	31	31	62
South Africa	10	10	20
Taiwan, Province of China	31	31	62
Thailand	29	32	61
Ukraine	76	76	152
United Kingdom	16	16	32
United States	559	559	1118
Height			
For this outcome measure, number of subjects evaluable were 1598 and 1597 for each arm, respectively.			
Units: centimeter (cm)			
arithmetic mean	168.1	167.6	
standard deviation	± 9.84	± 10.54	-
Weight			
Units: kilogram (kg)			
arithmetic mean	91.14	91.4	
standard deviation	± 19.832	± 21.319	-
Body Mass Index (BMI)			
For this outcome measure, number of subjects evaluable were 1598 and 1597 for each arm, respectively.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	32.14	32.45	
standard deviation	± 6.107	± 7.497	-
Duration of Diabetes			
For this outcome measure, number of subjects evaluable were 1602 and 1602 for each arm, respectively.			
Units: years			

arithmetic mean	13.583	13.333	
standard deviation	± 8.409	± 8.321	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Fasiglifam placebo-matching tablet, orally, once daily for up to 588 days.	
Reporting group title	Fasiglifam 50 mg
Reporting group description:	
Fasiglifam 50 mg, tablet, orally, once daily for up to 582 days.	

Primary: Time to First Occurrence of Any Component of Primary Major Adverse Cardiovascular Event (MACE) Composite

End point title	Time to First Occurrence of Any Component of Primary Major Adverse Cardiovascular Event (MACE) Composite[1]

End point description:

The time from randomization to the first occurrences of any event in the primary MACE composite was evaluated using Kaplan-Meier analysis. The primary MACE composite comprised cardiovascular (CV) death, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for unstable angina (with or without revascularization). Full Analysis Set (FAS) included all randomized subjects who had baseline and at least 1 post-baseline assessment. Here, '99999' reported for median and 95% confidence interval (CI) signifies not estimable. Median time and corresponding 95% confidence interval could not be reached since very low number of participants (<50%) had event related to any component of primary MACE composite.

End point type	Primary

End point timeframe:

Baseline up to end of study (up to Day 588)

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: Median time and associated confidence interval could not be reached for any treatment group. Hence, comparative statistics could not be performed.

End point values	Placebo	Fasiglifam 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1603	1604		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Any Component of Secondary Major Adverse Cardiovascular Event (MACE) Composite

End point title	Time to First Occurrence of Any Component of Secondary Major Adverse Cardiovascular Event (MACE) Composite

End point description:

The time from randomization to the first occurrences of any event in the secondary MACE composite was

evaluated using Kaplan-Meier analysis. The secondary MACE composite comprised CV death, nonfatal MI, and nonfatal stroke. FAS included all randomized subjects who had baseline and at least 1 post-baseline assessment. Here, '99999' reported for median and 95% CI signifies not estimable. Median time and corresponding 95% confidence interval could not be reached since very low number of participants (<50%) had event related to any component of secondary MACE composite.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to Day 588)

End point values	Placebo	Fasiglifam 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1603	1604		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug.

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Fasiglifam placebo-matching tablet, orally, once daily for up to 588 days.

Reporting group title	Fasiglifam 50 mg

Reporting group description:

Fasiglifam 50 mg, tablet, orally, once daily for up to 582 days.

Serious adverse events	Placebo	Fasiglifam 50 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	197 / 1603 (12.29%)	201 / 1601 (12.55%)	
number of deaths (all causes)	13	12	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone cancer metastatic			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer stage IV			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic cancer			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine benign neoplasm			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant melanoma			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic neoplasm			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			

subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transitional cell carcinoma			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	2 / 1603 (0.12%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 1603 (0.06%)	5 / 1601 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 1603 (0.00%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 1603 (0.12%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	3 / 1603 (0.19%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary arterial stent insertion			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary revascularisation			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot amputation			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest discomfort			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	6 / 1603 (0.37%)	8 / 1601 (0.50%)	
occurrences causally related to treatment / all	0 / 6	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device pain			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 1603 (0.19%)	4 / 1601 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 1603 (0.06%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 1603 (0.12%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
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	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 1603 (0.12%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delusion			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychogenic seizure			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Angiogram			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 1603 (0.12%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
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 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 1603 (0.19%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	9 / 1603 (0.56%)	12 / 1601 (0.75%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	7 / 1603 (0.44%)	9 / 1601 (0.56%)	
occurrences causally related to treatment / all	0 / 8	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	5 / 1603 (0.31%)	7 / 1601 (0.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 1603 (0.00%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	4 / 1603 (0.25%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	3 / 1603 (0.19%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 1603 (0.06%)	4 / 1601 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 4	
Cardiac disorder			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 1603 (0.12%)	4 / 1601 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	7 / 1603 (0.44%)	12 / 1601 (0.75%)	
occurrences causally related to treatment / all	2 / 7	2 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 1603 (0.12%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	7 / 1603 (0.44%)	6 / 1601 (0.37%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	5 / 1603 (0.31%)	4 / 1601 (0.25%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	4 / 1603 (0.25%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Right ventricular failure			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid arteriosclerosis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central pain syndrome			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	7 / 1603 (0.44%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 1603 (0.31%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1603 (0.06%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 1603 (0.06%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Retinal haemorrhage			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1603 (0.12%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic calcification			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 1603 (0.12%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 1603 (0.06%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 1603 (0.12%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 1603 (0.12%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	3 / 1603 (0.19%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail bed inflammation			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder prolapse			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	4 / 1603 (0.25%)	6 / 1601 (0.37%)	
occurrences causally related to treatment / all	2 / 4	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	6 / 1603 (0.37%)	11 / 1601 (0.69%)	
occurrences causally related to treatment / all	1 / 6	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	2 / 1603 (0.12%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Pituitary haemorrhage			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gouty arthritis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 1603 (0.00%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1603 (0.06%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 1603 (0.12%)	6 / 1601 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 1603 (0.06%)	4 / 1601 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 1603 (0.31%)	7 / 1601 (0.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 1603 (0.12%)	3 / 1601 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal urinary tract infection			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 1603 (0.06%)	2 / 1601 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 1603 (0.06%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 1603 (0.06%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 1603 (0.12%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 1603 (0.12%)	0 / 1601 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	4 / 1603 (0.25%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	4 / 1603 (0.25%)	5 / 1601 (0.31%)	
occurrences causally related to treatment / all	3 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 1603 (0.00%)	1 / 1601 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Fasiglifam 50 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	427 / 1603 (26.64%)	415 / 1601 (25.92%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 1603 (2.50%)	42 / 1601 (2.62%)	
occurrences (all)	40	43	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 1603 (1.87%)	39 / 1601 (2.44%)	
occurrences (all)	31	45	
Headache			
subjects affected / exposed	32 / 1603 (2.00%)	41 / 1601 (2.56%)	
occurrences (all)	37	46	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 1603 (1.62%)	33 / 1601 (2.06%)	
occurrences (all)	26	34	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	48 / 1603 (2.99%)	44 / 1601 (2.75%)	
occurrences (all)	53	47	
Nausea			
subjects affected / exposed	35 / 1603 (2.18%)	33 / 1601 (2.06%)	
occurrences (all)	37	34	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 1603 (1.87%)	40 / 1601 (2.50%)	
occurrences (all)	34	43	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	36 / 1603 (2.25%)	41 / 1601 (2.56%)	
occurrences (all)	37	43	
Infections and infestations			
Bronchitis			
subjects affected / exposed	45 / 1603 (2.81%)	49 / 1601 (3.06%)	
occurrences (all)	51	53	
Influenza			
subjects affected / exposed	37 / 1603 (2.31%)	34 / 1601 (2.12%)	
occurrences (all)	41	34	
Nasopharyngitis			
subjects affected / exposed	55 / 1603 (3.43%)	61 / 1601 (3.81%)	
occurrences (all)	62	69	
Sinusitis			
subjects affected / exposed	36 / 1603 (2.25%)	22 / 1601 (1.37%)	
occurrences (all)	44	26	
Upper respiratory tract infection			
subjects affected / exposed	87 / 1603 (5.43%)	75 / 1601 (4.68%)	
occurrences (all)	107	85	
Urinary tract infection			
subjects affected / exposed	43 / 1603 (2.68%)	35 / 1601 (2.19%)	
occurrences (all)	51	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2012	• Clarified that study drug could be temporarily suspended and reinitiated and that subjects who temporarily suspended or permanently discontinued study drug could continue in the study and follow the schedule of study procedures unless they explicitly withdrew consent; and to clarify options for continued study participation that were to be offered to subjects who voluntarily withdrew. • Tests for urine albumin, protein, and creatinine were changed from qualitative to quantitative to allow calculation of albumin/creatinine and protein/creatinine ratios
13 November 2012	• Indicated which subjects with elevated liver enzyme results or elevated liver enzyme and liver function test (LFT) results should be referred to a hepatologist, based on a recommendation from the German Central Ethics Committee.
03 April 2013	• Clarified that only abnormal liver enzyme results (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 times the upper limit of normal [ULN] in a subject with normal baseline ALT or AST; ALT or AST >5*ULN and 2-fold greater than baseline in a subject with elevated baseline ALT or AST) that occurred on 2 consecutive occasions were to be reported as an adverse event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 December 2013	Following completion of the first phase 3 study (TAK-875_301), and after careful consideration of the data emerging from all the clinical studies and in consultation with the data monitoring committee (DMC), the Liver Safety Evaluation Committee, and the Executive Committee overseeing the fasiglifam CV outcomes trial (TAK-875_306), Takeda concluded that based on all available information, the benefits of treating subjects with fasiglifam do not outweigh the potential risks, thus Takeda decided voluntarily to terminate all development activities for fasiglifam based on liver safety concerns.	-

Notes:

Limitations and caveats

None reported