Clinical trial results:
A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAVENOUS CR845 IN HEMODIALYSIS PATIENTS WITH MODERATE-TO-SEVERE PRURITUS, WITH A 52-WEEK OPEN-LABEL EXTENSION

Summary

EudraCT number	2018-001930-17
Trial protocol	HU CZ GB PL
Global end of trial date	30 March 2020

Results information

Result version number	v1 (current)
This version publication date	10 October 2021
First version publication date	10 October 2021

Trial information

Trial identification

Sponsor protocol code	CR845-CLIN3103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03636269
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cara Therapeutics, Inc.
Sponsor organisation address	107 Elm Street, 9th Floor, Stamford, United States, 06902
Public contact	Regulatory Affairs, Icon clinical Research Ltd, 44 07831653684, markas.marriott@iconplc.com
Scientific contact	Regulatory Affairs, Icon clinical Research Ltd, 44 07831653684, markas.marriott@iconplc.com
Sponsor organisation name	Cara Therapeutics, Inc.
Sponsor organisation address	107 Elm Street, 9th Floor, Stamford, United States, 06902
Public contact	Cara Clinical Trials, Cara Therapeutics, Inc., 1 203-406-3700, Cara Therapeutics, Inc., 1 203-406-3700,
Scientific contact	Cara Clinical Trials, Cara Therapeutics, Inc., 1 203-406-3700, Cara Therapeutics, Inc., 1 203-406-3700,

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	30 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2020
Global end of trial reached?	Yes
Global end of trial date	30 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of IV CR845 at a dose of 0.5 mcg/kg compared to placebo in reducing the intensity of itch in hemodialysis patients with moderate-to-severe pruritus.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 279
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Australia: 29
Worldwide total number of subjects	473
EEA total number of subjects	119

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)	300
From 65 to 84 years	167
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Screening Visit will occur within 7 to 28 days prior to randomization to assess eligibility.

Period 1

Period 1 title	Double-blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CR845

Arm description:

The ITT Population consisted of 473 subjects randomized to study treatment, 237 to difelikefalin and 236 to placebo. The Double-blind Safety Population consisted of 471 randomized subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period; 235 of these subjects were treated with difelikefalin, and 236 were treated with placebo. Two subjects were randomized to difelikefalin but did not receive any study drug.

Arm type	Experimental
Investigational medicinal product name	CR845
Investigational medicinal product code	
Other name	Difelikefalin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV CR845 0.5 mcg/kg administered after each dialysis session (3 times/week)

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV Placebo administered after each dialysis session (3 times/week)

Number of subjects in period 1	CR845	Placebo
Started	237	236
Completed	206	223
Not completed	31	13
Adverse event, serious fatal	2	1
Consent withdrawn by subject	5	1
Subject non-compliance	1	2
Adverse event, non-fatal	11	6
Eligibility (inclusion/exclusion criteria)	2	-
other	8	3
Lost to follow-up	1	-
Lack of efficacy	1	-

Period 2	
Period 2 title	Open-label Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	CR845

Arm description: -

Arm type	Experimental
Investigational medicinal product name	CR845
Investigational medicinal product code	
Other name	Difelikefalin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

IV CR845 0.5 mcg/kg administered after each dialysis session (3 times/week)

Number of subjects in period 2[1]	CR845
Started	399
Completed	5
Not completed	394
Adverse event, serious fatal	13
Consent withdrawn by subject	11
Administrative	36

Adverse event, non-fatal	8
Eligibility (inclusion/exclusion criteria)	2
other	9
Stop-unrelated to safety or lack of drug effect	313
Lack of efficacy	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 399 subjects out of 473 randomized in the Double-blind Treatment Phase continued to
the Open-label Phase, of whom 210 were previously randomized to the placebo group and 189 were previously randomized to the difelikefalin, respectively.

Baseline characteristics

Reporting groups	
Reporting group title	CR845

Reporting group description:

The ITT Population consisted of 473 subjects randomized to study treatment, 237 to difelikefalin and 236 to placebo. The Double-blind Safety Population consisted of 471 randomized subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period; 235 of these subjects were treated with difelikefalin, and 236 were treated with placebo. Two subjects were randomized to difelikefalin but did not receive any study drug.

Reporting group title	Placebo

Reporting group description: -

Reporting group values	CR845	Placebo	Total
Number of subjects	237	236	473
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.7	59.6	
standard deviation	± 13.11	± 13.07	-
Gender categorical Units: Subjects			
Female	100	97	197
Male	137	139	276

End points

End points reporting groups

Reporting group title	CR845

Reporting group description:

The ITT Population consisted of 473 subjects randomized to study treatment, 237 to difelikefalin and 236 to placebo. The Double-blind Safety Population consisted of 471 randomized subjects who received at least 1 dose of double-blind study drug during the Double-blind Treatment Period; 235 of these subjects were treated with difelikefalin, and 236 were treated with placebo. Two subjects were randomized to difelikefalin but did not receive any study drug.

Reporting group title	Placebo

Reporting group description: -

Reporting group title	CR845

Reporting group description: -

Primary: Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (NRS) score at Week 12

End point title	Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (NRS) score at Week 12

End point description:

End point type	Primary

End point timeframe:

Week 12

End point values	CR845	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	236		
Units: Percentage				
least squares mean (confidence interval 54%)	54.0 (43.9 to 63.9)	42.2 (32.5 to 52.5)		

Statistical analyses

Statistical analysis title	LS means estimate of percent with improvement

Statistical analysis description:

Estimated percentage, odds ratio and P value used a logistic regression model with terms for treatment group,
baseline NRS score, region, use of anti-itch medication during the week prior to randomization, and the presence
of specific medical conditions. Missing values were imputed using MI under MAR missing data assumption for
interim subjects and post-interim subjects separately.

Comparison groups	CR845 v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	CHW = Cui, Hung, Wang
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.41

Secondary: Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline ≥4 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12

End point title	Reduction of itch intensity as assessed by the proportion of patients achieving an improvement from baseline ≥4 points with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score at Week 12

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	CR845	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237[1]	236		
Units: Percentage				
least squares mean (confidence interval 41.2%)	41.2 (33.0 to 55.0)	28.4 (21.3 to 36.7)		

Notes:

[1] - 2 Subjects were randomized to CR845 but did not receive CR845

Statistical analyses

Statistical analysis title	LS means estimate of percent with improvement
Comparison groups	CR845 v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Cui, Hung, Wang
Parameter estimate	Odds ratio (OR)
Point estimate	1.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	2.74

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of adverse event reporting started after the signing of the ICF through the study follow-up visit or early termination visit (or 7-10 days after the last dose if no early termination visit was conducted).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Subjects in CR845 Group in Double-blind Portion
Reporting group description: -	
Reporting group title	Subjects in Placebo Group in Double-blind Portion
Reporting group description: -	
Reporting group title	Subjects in CR845 Open-label Portion

Reporting group description: -

Serious adverse events	Subjects in CR845 Group in Double-blind Portion	Subjects in Placebo Group in Double-blind Portion	Subjects in CR845 Open-label Portion
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 235 (24.68%)	51 / 236 (21.61%)	130 / 399 (32.58%)
number of deaths (all causes)	2	2	15
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric neoplasm			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 235 (0.00%)	5 / 236 (2.12%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	3 / 235 (1.28%)	1 / 236 (0.42%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 235 (0.00%)	3 / 236 (1.27%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 235 (0.00%)	2 / 236 (0.85%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			

subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry gangrene			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abdominal hernia repair			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter placement			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple drug therapy			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	8 / 235 (3.40%)	1 / 236 (0.42%)	10 / 399 (2.51%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 235 (0.85%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peripheral swelling			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 235 (1.70%)	2 / 236 (0.85%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 235 (0.43%)	1 / 236 (0.42%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 235 (0.85%)	0 / 236 (0.00%)	7 / 399 (1.75%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	3 / 235 (1.28%)	0 / 236 (0.00%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest X-ray abnormal			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paracentesis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bleeding time prolonged			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 235 (0.00%)	3 / 236 (1.27%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access malfunction			
subjects affected / exposed	1 / 235 (0.43%)	2 / 236 (0.85%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	6 / 399 (1.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site haemorrhage			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft thrombosis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibula fracture			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access complication			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft complication			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site haemorrhage			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall wound			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femoral neck fracture			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured ischium			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodialysis complication			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access site thrombosis			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 235 (0.43%)	2 / 236 (0.85%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 235 (0.85%)	0 / 236 (0.00%)	5 / 399 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 235 (0.43%)	1 / 236 (0.42%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiac failure			
subjects affected / exposed	2 / 235 (0.85%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute coronary syndrome			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Acute left ventricular failure			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 235 (0.43%)	1 / 236 (0.42%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			

subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive encephalopathy			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amnesia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delayed ischaemic neurological deficit			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 235 (0.85%)	4 / 236 (1.69%)	6 / 399 (1.50%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 235 (0.43%)	2 / 236 (0.85%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	4 / 399 (1.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 235 (0.85%)	0 / 236 (0.00%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Impaired gastric emptying			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Alcoholic pancreatitis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gastroparesis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polyps			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Pneumobilia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatic failure			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Diabetic foot			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioedema			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
End stage renal disease			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nephrolithiasis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 235 (1.28%)	4 / 236 (1.69%)	14 / 399 (3.51%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Cellulitis			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	4 / 399 (1.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 235 (0.85%)	1 / 236 (0.42%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 235 (0.00%)	2 / 236 (0.85%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	2 / 235 (0.85%)	0 / 236 (0.00%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 235 (1.28%)	0 / 236 (0.00%)	22 / 399 (5.51%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abscess limb			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site cellulitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	3 / 399 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cyst infection			

subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site cellulitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	4 / 399 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin infection			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	2 / 399 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 235 (0.00%)	1 / 236 (0.42%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysematous cystitis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	0 / 399 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia escherichia			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	4 / 235 (1.70%)	3 / 236 (1.27%)	4 / 399 (1.00%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 235 (0.00%)	2 / 236 (0.85%)	6 / 399 (1.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 235 (0.43%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calciphylaxis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Decreased appetite			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketosis			

subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 235 (0.00%)	0 / 236 (0.00%)	1 / 399 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Subjects in CR845 Group in Double-blind Portion	Subjects in Placebo Group in Double-blind Portion	Subjects in CR845 Open-label Portion
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 235 (23.83%)	43 / 236 (18.22%)	204 / 399 (51.13%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	14 / 235 (5.96%)	11 / 236 (4.66%)	52 / 399 (13.03%)
occurrences (all)	15	11	61
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 235 (3.83%)	4 / 236 (1.69%)	25 / 399 (6.27%)
occurrences (all)	10	4	40
Hypertension			
subjects affected / exposed	6 / 235 (2.55%)	10 / 236 (4.24%)	24 / 399 (6.02%)
occurrences (all)	11	17	40
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 235 (5.11%)	12 / 236 (5.08%)	31 / 399 (7.77%)
occurrences (all)	13	14	36
Headache			

subjects affected / exposed	10 / 235 (4.26%)	6 / 236 (2.54%)	20 / 399 (5.01%)
occurrences (all)	10	6	21
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	18 / 235 (7.66%)	12 / 236 (5.08%)	45 / 399 (11.28%)
occurrences (all)	22	13	55
Vomiting			
subjects affected / exposed	15 / 235 (6.38%)	13 / 236 (5.51%)	36 / 399 (9.02%)
occurrences (all)	19	14	45
Nausea			
subjects affected / exposed	15 / 235 (6.38%)	10 / 236 (4.24%)	37 / 399 (9.27%)
occurrences (all)	19	11	43
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	8 / 235 (3.40%)	5 / 236 (2.12%)	20 / 399 (5.01%)
occurrences (all)	9	5	26
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 235 (1.28%)	5 / 236 (2.12%)	22 / 399 (5.51%)
occurrences (all)	3	5	26

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2019	Update protocol to global amendment
12 July 2019	Modify the order of the secondary endpoints
10 September 2019	Analysis of treatment effect at specific early timepoints, Week 4 and Week 8, has been added as secondary efficacy endpoints, and an adjustment for multiplicity will be implemented to protect the overall Type 1 error. Change from baseline at Week 12 for the Skindex-10 Scale total score and the 5-D Itch Scale total score will be analyzed using an analysis of covariance (ANCOVA) model.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported