Clinical trial results:
A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study of NEOD001 Plus Standard of Care vs. Placebo Plus Standard of Care in Subjects with Light Chain (AL) Amyloidosis

Summary

EudraCT number	2014-003865-11
Trial protocol	DE AT ES BE NL FR GB GR PL DK IT
Global end of trial date	08 June 2018

Results information

Result version number	v1 (current)
This version publication date	28 March 2019
First version publication date	28 March 2019

Trial information

Trial identification

Sponsor protocol code	NEOD001-CL002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02312206
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Prothena Therapeutics Limited, now merged into Prothena Biosciences Limited
Sponsor organisation address	77 Sir John Rogerson's Quay, Block C, Grand Canal Docklands, Dublin 2, Ireland, D02 T804
Public contact	Communications Office, Prothena Biosciences Inc, info@prothena.com
Scientific contact	Clinical Trials Office, Prothena Biosciences Inc, info@prothena.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	30 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2018
Global end of trial reached?	Yes
Global end of trial date	08 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of NEOD001 plus standard of care (SOC) vs. placebo plus standard of care when administered intravenously in subjects with AL amyloidosis by assessing time to all- cause mortality or cardiac hospitalization

Protection of trial subjects:

This study was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice, the principles of the Declaration of Helsinki, and with the laws of the countries in which the study was conducted. The Investigator had the ability to break the blind for a specific subject in the event of an immediate medical emergency, wherein knowledge of the subject's treatment (NEOD001 or placebo) needed to be known in order to provide adequate medical treatment. In these situations, the breaking of the blind was to be reported to the Sponsor or its designee within 24 hours. An independent DMC was in place to safeguard the interests of subjects in the study and to help ensure the integrity and credibility of the study.

Background therapy:

All subjects received concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion. Antiviral prophylaxis was required.

Evidence for comparator: -

Actual start date of recruitment	27 April 2015
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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 3

Country: Number of subjects enrolled	United States: 142
Worldwide total number of subjects	260
EEA total number of subjects	92

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	139
From 65 to 84 years	117
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 260 subjects were enrolled in the study, 130 randomly assigned to receive NEOD001 and 130 randomly assigned to receive placebo.

Pre-assignment

Screening details:

Screening evaluations and procedures were performed within 28 days prior to the first study drug administration on Month 1-Day 1. Individual test results that did not meet eligibility requirements could be repeated, with the exception of 6MWT; full rescreening was only allowed once per subject.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	NEOD001 24 mg/kg plus SOC

Arm description:

NEOD001, 24 mg/kg IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator’s discretion.

Arm type	Experimental
Investigational medicinal product name	NEOD001 24 mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug administered intravenously every 4 weeks for 12 months, starting at the Month 1-Day 1 Visit.

Arm title	Placebo plus SOC

Arm description:

Placebo, 0.9% Saline IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator’s discretion.

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

Dosage and administration details:

Intravenous drip use (Noncurrent)

Number of subjects in period 1	NEOD001 24 mg/kg plus SOC	Placebo plus SOC
Started	130	130
Informed Consent Obtained	130	130
Not Completed	130	130
Completed	0	0
Not completed	130	130
Adverse event, serious fatal	1	-
Consent withdrawn by subject	7	6
Physician decision	7	6
Disease progression	1	-
Patient progression and institution of new therapy	1	-
Subject missed three consecutive treatment visits	-	1
Adverse event, non-fatal	2	6
Death	30	36
Study Terminated by Sponsor	81	74
Patient transferred to hospice	-	1

Baseline characteristics

Reporting groups	
Reporting group title	NEOD001 24 mg/kg plus SOC
Reporting group description:	
NEOD001, 24 mg/kg IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.	
Reporting group title	Placebo plus SOC
Reporting group description:	
Placebo, 0.9% Saline IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.	

Reporting group values	NEOD001 24 mg/kg plus SOC	Placebo plus SOC	Total
Number of subjects	130	130	260
Age categorical Units: Subjects			
Adults (18-64 years)	69	70	139
From 65-84 years	61	56	117
85 years and over	0	4	4
Age continuous Units: years			
arithmetic mean	63.69	63.24	
standard deviation	± 9.478	± 9.708	-
Gender categorical Units: Subjects			
Female	48	40	88
Male	82	90	172
Race Units: Subjects			
White	118	120	238
Black or African American	9	3	12
Not reported	1	5	6
Asian	2	2	4
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	116	122	238
Not reported	12	6	18

Subject analysis sets	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population includes all subjects who received any amount of study drug	
Subject analysis set title	Placebo plus SOC (Safety Population)

Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Population includes all subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	Placebo plus SOC (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	Placebo plus SOC (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (PN Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score >= 2 and at least one postbaseline NIS-LL total score assessment	
Subject analysis set title	Placebo plus SOC (PN Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score >= 2 and at least one postbaseline NIS-LL total score assessment	

Reporting group values	NEOD001 24 mg/kg plus SOC (Safety Population)	Placebo plus SOC (Safety Population)	NEOD001 24 mg/kg plus SOC (ITT Population)
Number of subjects	130	130	130
Age categorical Units: Subjects			
Adults (18-64 years)	69	70	69
From 65-84 years	61	56	61
85 years and over	0	4	0
Age continuous Units: years			
arithmetic mean	63.69	63.24	63.69
standard deviation	± 9.478	± 9.708	± 9.478
Gender categorical Units: Subjects			
Female	48	40	48
Male	82	90	82
Race Units: Subjects			
White	118	120	118

Black or African American	9	3	9
Not reported	1	5	1
Asian	2	2	2
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	2
Not Hispanic or Latino	116	122	116
Not reported	12	6	12

Reporting group values	Placebo plus SOC (ITT Population)	NEOD001 24 mg/kg plus SOC (Renal Evaluable Population)	Placebo plus SOC (Renal Evaluable Population)
Number of subjects	130	64	45
Age categorical Units: Subjects			
Adults (18-64 years)	70	34	28
From 65-84 years	56	30	16
85 years and over	4	0	1
Age continuous Units: years			
arithmetic mean	63.24	63.57	60.62
standard deviation	± 9.708	± 8.256	± 10.100
Gender categorical Units: Subjects			
Female	40	18	13
Male	90	46	32
Race Units: Subjects			
White	120	59	44
Black or African American	3	2	0
Not reported	5	1	1
Asian	2	2	0
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	0
Not Hispanic or Latino	122	56	43
Not reported	6	6	2

Reporting group values	NEOD001 24 mg/kg plus SOC (PN Evaluable Population)	Placebo plus SOC (PN Evaluable Population)	
Number of subjects	15	14	
Age categorical Units: Subjects			
Adults (18-64 years)	8	7	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65.13	64.56	
standard deviation	± 10.158	± 8.372	

Gender categorical Units: Subjects			
Female	2	3	
Male	13	11	
Race Units: Subjects			
White	15	13	
Black or African American	0	0	
Not reported	0	1	
Asian	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	14	14	
Not reported	1	0	

End points

End points reporting groups

Reporting group title	NEOD001 24 mg/kg plus SOC
Reporting group description:	
NEOD001, 24 mg/kg IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.	
Reporting group title	Placebo plus SOC
Reporting group description:	
Placebo, 0.9% Saline IV every 4 weeks with concomitant standard of care chemotherapy, which must have included bortezomib administered subcutaneously on a weekly basis for the initial, first-line chemotherapy regimen. Subsequent chemotherapy regimens may have been prescribed as per standard of care at the Investigator's discretion.	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population includes all subjects who received any amount of study drug	
Subject analysis set title	Placebo plus SOC (Safety Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Population includes all subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	Placebo plus SOC (ITT Population)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT Population includes all randomized subjects who received any amount of study drug	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	Placebo plus SOC (Renal Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Renal Evaluable Population includes all ITT subjects who had a baseline proteinuria >0.5 g/24 hours and at least one postbaseline assessment of 24 hour protein	
Subject analysis set title	NEOD001 24 mg/kg plus SOC (PN Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score >= 2 and at least one postbaseline NIS-LL total score assessment	
Subject analysis set title	Placebo plus SOC (PN Evaluable Population)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Peripheral Neuropathy (PN) Evaluable Population includes all ITT subjects who had ascending sensorimotor neuropathy due to AL amyloidosis at screening and had a baseline NIS-LL total score >= 2 and at least one postbaseline NIS-LL total score assessment	

Primary: Time to composite of all-cause mortality or cardiac hospitalization

End point title	Time to composite of all-cause mortality or cardiac hospitalization

End point description:

Time to all-cause mortality death occurring after the first infusion of study drug or cardiac hospitalization as adjudicated by the CEC occurring at least 91 days after a first infusion of study drug through last subject last visit, whichever came first

End point type	Primary

End point timeframe:

Randomization until the date of death or cardiac hospitalization

End point values	NEOD001 24 mg/kg plus SOC (ITT Population)	Placebo plus SOC (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130	130		
Units: Subjects				
Died or cardiac hospitalization - Yes	56	62		
Died or cardiac hospitalization - No	74	68		

Statistical analyses

Statistical analysis title	Time to comp. all-cause mortality or cardiac hosp

Statistical analysis description:

Test to determine if the survival distribution of the time-to all-cause mortality or cardiac hospitalization is the same or different between placebo and NEOD001.

Comparison groups	NEOD001 24 mg/kg plus SOC (ITT Population) v Placebo plus SOC (ITT Population)
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.835
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5799
upper limit	1.2011

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Initiation of study drug through the last study visit or up to 30 days after last dose, whichever is later.	
Adverse event reporting additional description:	
AE that newly appears, increases in frequency, or worsens in severity following initiation of study drug and through the last study visit or up to 30 days after date of last dose, whichever is later.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	NEOD001 24 mg/kg plus SOC
Reporting group description:	
NEOD001 24 mg/kg IV every 4 weeks	
Reporting group title	Placebo plus SOC
Reporting group description:	
Placebo, 0.9% Saline IV every 4 weeks	
Reporting group title	Total
Reporting group description:	
Total NEOD001 + Placebo	

Serious adverse events	NEOD001 24 mg/kg plus SOC	Placebo plus SOC	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 130 (67.69%)	91 / 130 (70.00%)	179 / 260 (68.85%)
number of deaths (all causes)	41	42	83
number of deaths resulting from adverse events	20	32	52
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	3 / 130 (2.31%)	6 / 130 (4.62%)	9 / 260 (3.46%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	2 / 130 (1.54%)	3 / 130 (2.31%)	5 / 260 (1.92%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	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	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 3
General physical health deterioration			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 130 (0.00%)	3 / 130 (2.31%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Oedema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			

subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Sudden death			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 4
Immune system disorders			
Amyloidosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 130 (2.31%)	0 / 130 (0.00%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	3 / 130 (2.31%)	0 / 130 (0.00%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 2	2 / 3	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infiltration			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pleural effusion			
subjects affected / exposed	2 / 130 (1.54%)	6 / 130 (4.62%)	8 / 260 (3.08%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Productive cough			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary amyloidosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Confusional state			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
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 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
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 necrosis marker increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Troponin T increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Procedural haemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Atrial fibrillation			
subjects affected / exposed	6 / 130 (4.62%)	6 / 130 (4.62%)	12 / 260 (4.62%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac amyloidosis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiac arrest			
subjects affected / exposed	9 / 130 (6.92%)	10 / 130 (7.69%)	19 / 260 (7.31%)
occurrences causally related to treatment / all	0 / 10	0 / 13	0 / 23
deaths causally related to treatment / all	0 / 5	0 / 6	0 / 11
Cardiac failure			
subjects affected / exposed	17 / 130 (13.08%)	28 / 130 (21.54%)	45 / 260 (17.31%)
occurrences causally related to treatment / all	0 / 35	0 / 35	0 / 70
deaths causally related to treatment / all	0 / 1	0 / 5	0 / 6
Cardiac failure acute			
subjects affected / exposed	6 / 130 (4.62%)	5 / 130 (3.85%)	11 / 260 (4.23%)
occurrences causally related to treatment / all	0 / 7	0 / 7	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure chronic			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	17 / 130 (13.08%)	9 / 130 (6.92%)	26 / 260 (10.00%)
occurrences causally related to treatment / all	0 / 19	0 / 11	0 / 30
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiogenic shock			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiopulmonary failure			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conduction disorder			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Coronary artery disease			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ventricular tachycardia			
subjects affected / exposed	2 / 130 (1.54%)	5 / 130 (3.85%)	7 / 260 (2.69%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	11 / 130 (8.46%)	7 / 130 (5.38%)	18 / 260 (6.92%)
occurrences causally related to treatment / all	0 / 12	0 / 9	0 / 21
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulation factor deficiency			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic pseudo-obstruction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	0 / 130 (0.00%)	3 / 130 (2.31%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric artery thrombosis			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
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	2 / 130 (1.54%)	2 / 130 (1.54%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic hepatic cyst			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hepatic haematoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatosplenomegaly			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	7 / 130 (5.38%)	9 / 130 (6.92%)	16 / 260 (6.15%)
occurrences causally related to treatment / all	0 / 8	0 / 10	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 130 (1.54%)	4 / 130 (3.08%)	6 / 260 (2.31%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Urinary retention			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscle spasms			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
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 infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 130 (0.00%)	3 / 130 (2.31%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Injection site cellulitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	3 / 130 (2.31%)	0 / 130 (0.00%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	3 / 130 (2.31%)	4 / 130 (3.08%)	7 / 260 (2.69%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pasteurella infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	11 / 130 (8.46%)	9 / 130 (6.92%)	20 / 260 (7.69%)
occurrences causally related to treatment / all	0 / 16	0 / 10	0 / 26
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Pneumonia viral			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	3 / 130 (2.31%)	2 / 130 (1.54%)	5 / 260 (1.92%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Septic shock			
subjects affected / exposed	4 / 130 (3.08%)	1 / 130 (0.77%)	5 / 260 (1.92%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 4	0 / 1	0 / 5
Soft tissue infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	4 / 260 (1.54%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	0 / 130 (0.00%)	3 / 130 (2.31%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	5 / 130 (3.85%)	4 / 130 (3.08%)	9 / 260 (3.46%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	3 / 260 (1.15%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	1 / 260 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	5 / 130 (3.85%)	3 / 130 (2.31%)	8 / 260 (3.08%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			

subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	2 / 260 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
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	NEOD001 24 mg/kg plus SOC	Placebo plus SOC	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 130 (93.85%)	123 / 130 (94.62%)	245 / 260 (94.23%)
Vascular disorders			
Hypotension			
subjects affected / exposed	20 / 130 (15.38%)	29 / 130 (22.31%)	49 / 260 (18.85%)
occurrences (all)	29	54	83
Orthostatic hypotension			
subjects affected / exposed	9 / 130 (6.92%)	13 / 130 (10.00%)	22 / 260 (8.46%)
occurrences (all)	13	13	26
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 130 (6.92%)	9 / 130 (6.92%)	18 / 260 (6.92%)
occurrences (all)	18	10	28
Chills			
subjects affected / exposed	9 / 130 (6.92%)	4 / 130 (3.08%)	13 / 260 (5.00%)
occurrences (all)	11	4	15
Fatigue			
subjects affected / exposed	57 / 130 (43.85%)	52 / 130 (40.00%)	109 / 260 (41.92%)
occurrences (all)	125	90	215
Oedema peripheral			
subjects affected / exposed	55 / 130 (42.31%)	56 / 130 (43.08%)	111 / 260 (42.69%)
occurrences (all)	112	88	200
Pyrexia			
subjects affected / exposed	12 / 130 (9.23%)	11 / 130 (8.46%)	23 / 260 (8.85%)
occurrences (all)	18	13	31
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	31 / 130 (23.85%)	27 / 130 (20.77%)	58 / 260 (22.31%)
occurrences (all)	46	33	79
Dyspnoea			
subjects affected / exposed	38 / 130 (29.23%)	40 / 130 (30.77%)	78 / 260 (30.00%)
occurrences (all)	63	68	131
Dyspnoea exertional			
subjects affected / exposed	11 / 130 (8.46%)	7 / 130 (5.38%)	18 / 260 (6.92%)
occurrences (all)	13	13	26
Epistaxis			
subjects affected / exposed	8 / 130 (6.15%)	7 / 130 (5.38%)	15 / 260 (5.77%)
occurrences (all)	9	7	16
Pleural effusion			
subjects affected / exposed	8 / 130 (6.15%)	13 / 130 (10.00%)	21 / 260 (8.08%)
occurrences (all)	10	15	25
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 130 (8.46%)	3 / 130 (2.31%)	14 / 260 (5.38%)
occurrences (all)	11	3	14
Depression			
subjects affected / exposed	11 / 130 (8.46%)	7 / 130 (5.38%)	18 / 260 (6.92%)
occurrences (all)	13	8	21
Insomnia			
subjects affected / exposed	39 / 130 (30.00%)	30 / 130 (23.08%)	69 / 260 (26.54%)
occurrences (all)	41	35	76
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 130 (3.85%)	8 / 130 (6.15%)	13 / 260 (5.00%)
occurrences (all)	5	10	15
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 130 (8.46%)	8 / 130 (6.15%)	19 / 260 (7.31%)
occurrences (all)	13	14	27
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 130 (9.23%)	5 / 130 (3.85%)	17 / 260 (6.54%)
occurrences (all)	36	7	43
Blood creatinine increased			

subjects affected / exposed	22 / 130 (16.92%)	11 / 130 (8.46%)	33 / 260 (12.69%)
occurrences (all)	55	21	76
Platelet count decreased			
subjects affected / exposed	4 / 130 (3.08%)	10 / 130 (7.69%)	14 / 260 (5.38%)
occurrences (all)	11	20	31
Weight decreased			
subjects affected / exposed	19 / 130 (14.62%)	16 / 130 (12.31%)	35 / 260 (13.46%)
occurrences (all)	25	23	48
Weight increased			
subjects affected / exposed	6 / 130 (4.62%)	11 / 130 (8.46%)	17 / 260 (6.54%)
occurrences (all)	12	12	24
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	8 / 130 (6.15%)	10 / 130 (7.69%)	18 / 260 (6.92%)
occurrences (all)	10	12	22
Fall			
subjects affected / exposed	14 / 130 (10.77%)	10 / 130 (7.69%)	24 / 260 (9.23%)
occurrences (all)	18	14	32
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 130 (6.15%)	10 / 130 (7.69%)	18 / 260 (6.92%)
occurrences (all)	10	15	25
Cardiac failure			
subjects affected / exposed	9 / 130 (6.92%)	6 / 130 (4.62%)	15 / 260 (5.77%)
occurrences (all)	13	6	19
Palpitations			
subjects affected / exposed	3 / 130 (2.31%)	11 / 130 (8.46%)	14 / 260 (5.38%)
occurrences (all)	3	15	18
Nervous system disorders			
Dizziness			
subjects affected / exposed	25 / 130 (19.23%)	38 / 130 (29.23%)	63 / 260 (24.23%)
occurrences (all)	35	54	89
Dysgeusia			
subjects affected / exposed	10 / 130 (7.69%)	12 / 130 (9.23%)	22 / 260 (8.46%)
occurrences (all)	12	12	24
Headache			

subjects affected / exposed	17 / 130 (13.08%)	16 / 130 (12.31%)	33 / 260 (12.69%)
occurrences (all)	20	21	41
Neuropathy peripheral			
subjects affected / exposed	30 / 130 (23.08%)	17 / 130 (13.08%)	47 / 260 (18.08%)
occurrences (all)	43	27	70
Paraesthesia			
subjects affected / exposed	10 / 130 (7.69%)	13 / 130 (10.00%)	23 / 260 (8.85%)
occurrences (all)	14	18	32
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 130 (10.77%)	13 / 130 (10.00%)	27 / 260 (10.38%)
occurrences (all)	23	23	46
Syncope			
subjects affected / exposed	7 / 130 (5.38%)	11 / 130 (8.46%)	18 / 260 (6.92%)
occurrences (all)	10	17	27
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 130 (16.15%)	27 / 130 (20.77%)	48 / 260 (18.46%)
occurrences (all)	43	67	110
Lymphopenia			
subjects affected / exposed	6 / 130 (4.62%)	7 / 130 (5.38%)	13 / 260 (5.00%)
occurrences (all)	19	18	37
Thrombocytopenia			
subjects affected / exposed	10 / 130 (7.69%)	9 / 130 (6.92%)	19 / 260 (7.31%)
occurrences (all)	17	19	36
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	15 / 130 (11.54%)	15 / 130 (11.54%)	30 / 260 (11.54%)
occurrences (all)	23	17	40
Abdominal pain			
subjects affected / exposed	13 / 130 (10.00%)	15 / 130 (11.54%)	28 / 260 (10.77%)
occurrences (all)	19	16	35
Abdominal pain upper			
subjects affected / exposed	6 / 130 (4.62%)	8 / 130 (6.15%)	14 / 260 (5.38%)
occurrences (all)	6	8	14
Constipation			

subjects affected / exposed	55 / 130 (42.31%)	55 / 130 (42.31%)	110 / 260 (42.31%)
occurrences (all)	75	82	157
Diarrhoea			
subjects affected / exposed	51 / 130 (39.23%)	54 / 130 (41.54%)	105 / 260 (40.38%)
occurrences (all)	110	82	192
Nausea			
subjects affected / exposed	56 / 130 (43.08%)	43 / 130 (33.08%)	99 / 260 (38.08%)
occurrences (all)	86	71	157
Stomatitis			
subjects affected / exposed	7 / 130 (5.38%)	8 / 130 (6.15%)	15 / 260 (5.77%)
occurrences (all)	7	9	16
Vomiting			
subjects affected / exposed	27 / 130 (20.77%)	20 / 130 (15.38%)	47 / 260 (18.08%)
occurrences (all)	42	32	74
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 130 (5.38%)	7 / 130 (5.38%)	14 / 260 (5.38%)
occurrences (all)	7	7	14
Ecchymosis			
subjects affected / exposed	7 / 130 (5.38%)	8 / 130 (6.15%)	15 / 260 (5.77%)
occurrences (all)	7	8	15
Pruritus			
subjects affected / exposed	14 / 130 (10.77%)	12 / 130 (9.23%)	26 / 260 (10.00%)
occurrences (all)	19	14	33
Rash			
subjects affected / exposed	15 / 130 (11.54%)	18 / 130 (13.85%)	33 / 260 (12.69%)
occurrences (all)	16	24	40
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 130 (6.92%)	4 / 130 (3.08%)	13 / 260 (5.00%)
occurrences (all)	16	9	25
Chronic kidney disease			
subjects affected / exposed	7 / 130 (5.38%)	6 / 130 (4.62%)	13 / 260 (5.00%)
occurrences (all)	17	10	27
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	12 / 130 (9.23%)	6 / 130 (4.62%)	18 / 260 (6.92%)
occurrences (all)	18	7	25
Back pain			
subjects affected / exposed	15 / 130 (11.54%)	12 / 130 (9.23%)	27 / 260 (10.38%)
occurrences (all)	17	12	29
Muscle spasms			
subjects affected / exposed	15 / 130 (11.54%)	7 / 130 (5.38%)	22 / 260 (8.46%)
occurrences (all)	17	8	25
Muscular weakness			
subjects affected / exposed	9 / 130 (6.92%)	5 / 130 (3.85%)	14 / 260 (5.38%)
occurrences (all)	12	9	21
Pain in extremity			
subjects affected / exposed	14 / 130 (10.77%)	8 / 130 (6.15%)	22 / 260 (8.46%)
occurrences (all)	16	11	27
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 130 (6.15%)	10 / 130 (7.69%)	18 / 260 (6.92%)
occurrences (all)	9	14	23
Pneumonia			
subjects affected / exposed	8 / 130 (6.15%)	8 / 130 (6.15%)	16 / 260 (6.15%)
occurrences (all)	11	8	19
Upper respiratory tract infection			
subjects affected / exposed	23 / 130 (17.69%)	25 / 130 (19.23%)	48 / 260 (18.46%)
occurrences (all)	28	34	62
Urinary tract infection			
subjects affected / exposed	14 / 130 (10.77%)	6 / 130 (4.62%)	20 / 260 (7.69%)
occurrences (all)	17	8	25
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	27 / 130 (20.77%)	20 / 130 (15.38%)	47 / 260 (18.08%)
occurrences (all)	34	28	62
Hyperglycaemia			
subjects affected / exposed	8 / 130 (6.15%)	8 / 130 (6.15%)	16 / 260 (6.15%)
occurrences (all)	47	11	58
Hyperkalaemia			

subjects affected / exposed	9 / 130 (6.92%)	8 / 130 (6.15%)	17 / 260 (6.54%)
occurrences (all)	15	16	31
Hyperuricaemia			
subjects affected / exposed	9 / 130 (6.92%)	13 / 130 (10.00%)	22 / 260 (8.46%)
occurrences (all)	18	17	35
Hypoalbuminaemia			
subjects affected / exposed	7 / 130 (5.38%)	6 / 130 (4.62%)	13 / 260 (5.00%)
occurrences (all)	24	11	35
Hypokalaemia			
subjects affected / exposed	24 / 130 (18.46%)	26 / 130 (20.00%)	50 / 260 (19.23%)
occurrences (all)	72	47	119
Hyponatraemia			
subjects affected / exposed	16 / 130 (12.31%)	17 / 130 (13.08%)	33 / 260 (12.69%)
occurrences (all)	46	42	88

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2016	This global protocol amendment incorporates changes that were made during several country-specific amendments, which were issued between the finalization of Amendment 1 and this global Amendment 2.
06 November 2017	Overview of Major/Substantial Changes: Aligned with updated case report form and statistical analysis plan Removed requirement for monthly collection of additional coagulation indices Removed sample collection for quantitative/renal biomarkers Allowed postbaseline 6MWT to be administered on the same calendar day that study drug is administered Increased the number of subjects Clarified timing of serious adverse event collection

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported